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Breast Carcinoma in Situ Types, Diagnostics, Treatment and Prognosis

Charis Senkel, VI year, 5 group

Institute of Clinical Medicine, Clinic of Obstetrics and Gynaecology

Supervisor Prof. Dr. Rasa Vansevičiūtė-Petkevičienė

The Head of Department/Clinic Prof. Dr. Diana Ramašauskaitė

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charis.senkel@mf.stud.vu.lt

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Ductal breast carcinoma in Situ (0 stage of breast cancer)

Lobular breast carcinoma in Situ (risk factor of breast cancer)

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SUMMARY

Ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) represents premalignant diseases of the breast, typically localized in the milk ducts or in the terminal ducto-lobular unit. In difference to an invasive breast carcinoma there is no invasion of the basement membrane. While DCIS is considered as a precursor of invasive breast cancer, LCIS is a risk factor for breast cancer. Since implementation of mammography screening program the incidence of DCIS and LCIS has significantly increased. Both lesions, DCIS and LCIS, comprises a variety of heterogeneous subtypes with wide range of histomorphology, genetic abnormalities, biomarker expression profile and biological and clinical potential. The goal of therapy management with surgery, radiation therapy and endocrine therapy is to prevent local recurrence and progression to invasive disease. This is increasingly a great challenge to understand the natural history of in situ lesions and to find intelligent therapy concepts.

This review presents a summary for better understanding the heterogeneity of DCIS and LCIS and should show the current therapy management of these diseases. It highlights the need for de-escalation of therapy, especially for low-grade DCIS and LCIS variants to avoid over- and undertreatment.

Keywords: Ductal carcinoma in situ, Lobular carcinoma in situ, Lobular neoplasia, Risk stratification, Overtreatment

LITERATURE SOURCES

Published studies and scientific articles were identified and abstracted from MEDLINE via PubMed. I served manual searches of reference lists from systematic reviews. International Guidelines and recommendation of consensus conferences were sources for the review.
I include articles published between 2005 to 2022.

1. INTRODUCTION

Ductal carcinoma in situ (DCIS) or stage 0 breast cancer is a non-invasive breast cancer characterized by a neoplastic proliferation of epithelial cells confined within the basement membrane without evidence of invasion into surrounding tissue (1). Tumor cells proliferate at their original position in the breast milk ducts. As such, there is no risk for distant metastases or death. Disruption of the basement membrane layer would change the diagnosis from DCIS

to invasive breast cancer (IBC) (1). DCIS is considered to be a precursor for invasive breast cancer (2).
Specifically, the World Health Organization (WHO) defines the term DCIS as “a neoplastic proliferation of epithelial cells confined to the mammary ductal-lobular system and characterized by subtle to marked cytologic atypia and an inherent but not necessarily obligate tendency to progression to invasive breast cancer” (3).
Currently, DCIS comprises up to 20% - 25% of breast cancer diagnosis in the United States (1). More than 90% of DCIS cases are diagnosed by routine screening (4).
The diagnosis of DCIS does require a tissue biopsy. DCIS is a heterogeneous group of lesions that varies in the clinical presentation, genetics, biomarkers, morphologic features, as well as the clinical potential to progress to invasive breast cancer (1).
As heterogeneous as DCIS is, therapy management is still homogeneous today. The aim is to avoid overdiagnosis and overtreatment.
The treatment for DCIS is multidisciplinary and may include surgery, radiation therapy and/or endocrine therapy (1).

LCIS is a non-invasive, neoplastic proliferation of small, uniform, dyscohesive cells, which originates in the terminal duct lobular unit (TDLU) and fills and distends most of the acini of the involved lobule (3, 6).
It is described as a risk factor and nonobligate precursor of breast carcinoma.
The relative risk of invasive carcinoma after diagnosis of classic LCIS is approximately 9-10 times that of the general population (5). Characteristically, LCIS is multifocal and bilateral in a large proportion of cases (5).
LCIS will be found as an incidential finding on biopsy of the breast for other indications (5). There are no specific clinical or imaging findings (6). It has been observed in association with microcalcifications in up to 40% of cases that are diagnosed by core needle biopsy (5).

Lobular neoplasia (LN) of the breast includes both atypical lobular hyperplasia (ALH) and LCIS within the spectrum. ALH was subsequently introduced to describe morphologically similar but less well-developed lesions (7). Lobular neoplasia has also been termed lobular intraepithelial neoplasia (LIN), which divides these lesions using a 3-tiered grading scale based on extent and degree of lobular involvement and/or nuclear atypia (LIN1, LIN2 or LIN3) (7).

Lobular neoplasia and LIN nomenclatures have not been widely adopted and use of the terms ALH and LCIS is still prevalent in the literature (7).

Other morphologic subtypes of LCIS that are nonclassical include pleomorphic and florid (pleomorphic LCIS and florid LCIS). These LCIS variants are very similar to the pathological features of the DCIS and distinction can be difficult.
Therapy and treatment of LCIS depends on the risk of developing an invasive carcinoma and is a multidisciplinary decision.

2. EPIDEMIOLOGY

2.1 INCIDENCE DCIS

Before the implementation of mammographic screening program only 3% of all neoplasia were DCIS whereas today DCIS represents 20% - 25% of newly diagnosed breast cancer in the United States (1, 4) (Fig. 1).
Over 60,000 women were diagnosed with DCIS in the United States each year, 80% of all in situ breast lesions (2).
The risk of DCIS increases with age (11). It is uncommon in women younger than 30 years of age and has a higher rise among those older than 50 years of age (11). The rate of DCIS increases with age from 0.6 per 1000 screening examinations in women aged 40 to 49 years to 1.3 per 1000 screening examinations in women aged 70 to 84 years (11).
Women with DCIS have a 3-fold increased risk of dying of breast cancer compared with women without DCIS (9).
This mortality ratio of 3.36 based on Surveillance, Epidemiology, and End Results (SEER) based incidence and case-fatality rates (9). The risk is greater for young women and black women (9).
3.3 - 5.9% of women with DCIS carry a germline mutation in BRCA1 (BReast CAncer 1) or BRCA2 (BReast CAncer 2) and prevalence of BRCA mutation is significantly greater in women diagnosed with DCIS before age 50 and personal or family history of breast cancer (10, 11).
The incidence of DCIS has been relatively stable in the last five years (11), but there are trends because of the subtypes, heterogeneity of DCIS and differences in patients (age, social status, ancestry).

2.2 INCIDENCE LCIS

Classic LCIS usually is an incidental finding in a breast needle core biopsy or surgical excision specimen targeting another lesion (5). It is therefore difficult to estimate the actual incidence of LCIS (5). LCIS is identified in 0.5 - 1.5% of benign breast biopsies (5) and in 1.8 - 2.5% of all breast biopsies (5).

The incidence of LCIS in women without prior history of in situ or invasive breast carcinoma increased from 0.90/100,00 person-year in 1978 - 1980 to 3.19/100,00 person-year in 1996 - 1998 (12, 13). The increased incidence of LCIS is likely due to the increased use of mammographic screening and biopsy of mammographically indeterminate or suspicious lesions (5).

LCIS occurs predominantly in premenopausal women, with mean and median age at diagnosis of 49 and 50 years (5), 7 - 8 years younger than the DCIS (11).

LCIS is multicentric in 60 - 80% of patients and bilateral in 20 - 60% (6) (Fig. 1).

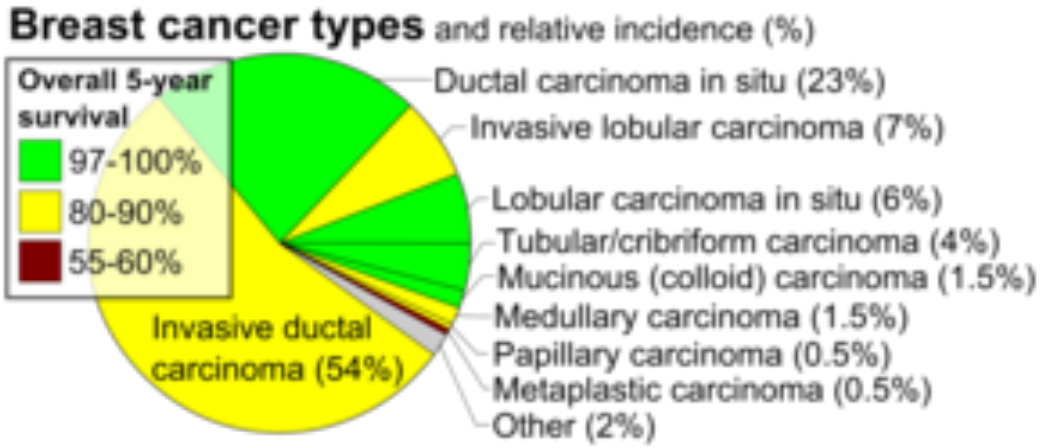

Figure 1: Histopathologic types of breast cancer, with relative incidences and prognoses. “Ductal carcinoma in situ” and “Lobular carcinoma in situ”.

2.3 MAMMOGRAPHIC SCREENING

Mammographic screening was introduced to reduce breast cancer mortality. The program is subject to strict quality controls and is evaluated regularly.

The widespread adoption of screening in United States, Europe and other developed countries dramatically increased the number of cases of DCIS and LCIS. 90% of all cases of DCIS are detected only in imaging studies (11).

Approximately one in every 1300 mammography examinations performed will lead to a diagnosis of DCIS, and it is estimated that 62,280 cases of DCIS will be diagnosed in 2009 in which the high-grade DCIS makes up the largest proportion (11).

LCIS usually is not visible on a mammogram (6). The condition is most often diagnosed as an incidential finding when you have a biopsy done (6).
So the incidence of LCIS increased indirect with adoption of mammographic screening program.

2.4 RISK FACTORS DCIS, LCIS

Risk factors for DCIS are largely similar to those for invasive breast cancer and includes modifiable factors and non-modifiable factors (10).

The risk profile and clinical history include: (1)
- age at menarche
- late age at menopause
- increasing age
- weight, elevated body mass index (> 25 kg/m2)
- nulliparity, age at birth of first child
- personal history of breast surgery of benign breast disease such as atypical hyperplasia
- history of breast cancer
- family history of breast cancer
- mammographically dense breast
- long-term use of postmenopausal estrogen and progestin therapy
- BRCA-1, BRCA-2 mutation carriers

The risk factors for LCIS are the same as for DCIS and invasive breast cancer. LCIS is more likely to occur in younger women and is more common in white women than in black women (6).

3. CLINICAL FEATURES

3.1 PATIENT PRESENTATION DCIS

DCIS does not generally cause symptoms. A few people with DCIS may notice a breast lump, itchy skin or nipple discharge (like blood) (10) but it is seen less frequently (10).
In most of the cases of DCIS, it is shown as a non-palpable mass and detected as microcalcifications in mammography (70 - 80%) (10).

3.2 IMAGING STUDIES DCIS

3.2.1 MAMMOGRAPHY

There are two types of mammograms to detect DCIS which are 2D and 3D.
A 2D mammogram is the most common imaging procedure used for detecting DCIS (14).
3D mammogram detects breast cancer more accurately, especially in dense breast tissue (14).
Interestingly, 3D mammography has not resulted in increased detection of DCIS (14).
Mammography is highly sensitive, and microcalcifications are found in 72 - 98% of DCIS (10). Calcifications can be due to DCIS but not all calcifications are found to be DCIS (14).
Many women develop benign calcifications in their breast when they are older.
In most mammography images, DCIS presents as microcalcifications of varying morphologies, such as amorphous, coarse, heterogeneous, or fine pleomorphic (16) (Fig. 2).
The fine pleomorphic morphology creates the highest suspicion for high-grade lesions (16).
The distribution of microcalcifications in the breast varies among the grouped, linear, and segmental forms (16).

3.2.2 ULTRASOUND

Ultrasound is not used on its own screening test. Ultrasound generally has limited utility in detecting DCIS (10). It is used to complete other screening tests.
DCIS lesions can effectively be recognized as mass-like lesions and non-mass like lesions by ultrasound (15). Hypoechoic areas and hypoechoic solid masses were the most common ultrasonographic features of DCIS (15). Ducts abnormalities and punctate echogenic foci were helpful for the diagnosis of DCIS (15) (Fig. 2).

3.2.3 MAGNETIC RESONANCE IMAGING

Breast MRI is currently being evaluated in DCIS. MRI is useful in the detection of DCIS, especially in high-grade DCIS even if some cases show a normal mammogram (16).
The sensitivity of MRI for detection of DCIS varies widely, from 60 - 100%, especially when high-resolution sequences are acquired but it may be useful for calcified or noncalcified carcinomas, as well as in the evaluation of tumor extend and of residual disease; in the identification of an occult primary tumor; in the detection of multifocal, multicentric, and contralateral tumors and in preoperative staging (16).

Pure DCIS lesions show non-nodular enhancement in 59% of cases, whereas 14% enhance a nodule, 14% do not enhance, and 12% presents as a focus (16). In contrast, 76% of the lesions associated with an invasive carcinoma and DCIS enhance as a nodule (16) (Fig. 2).

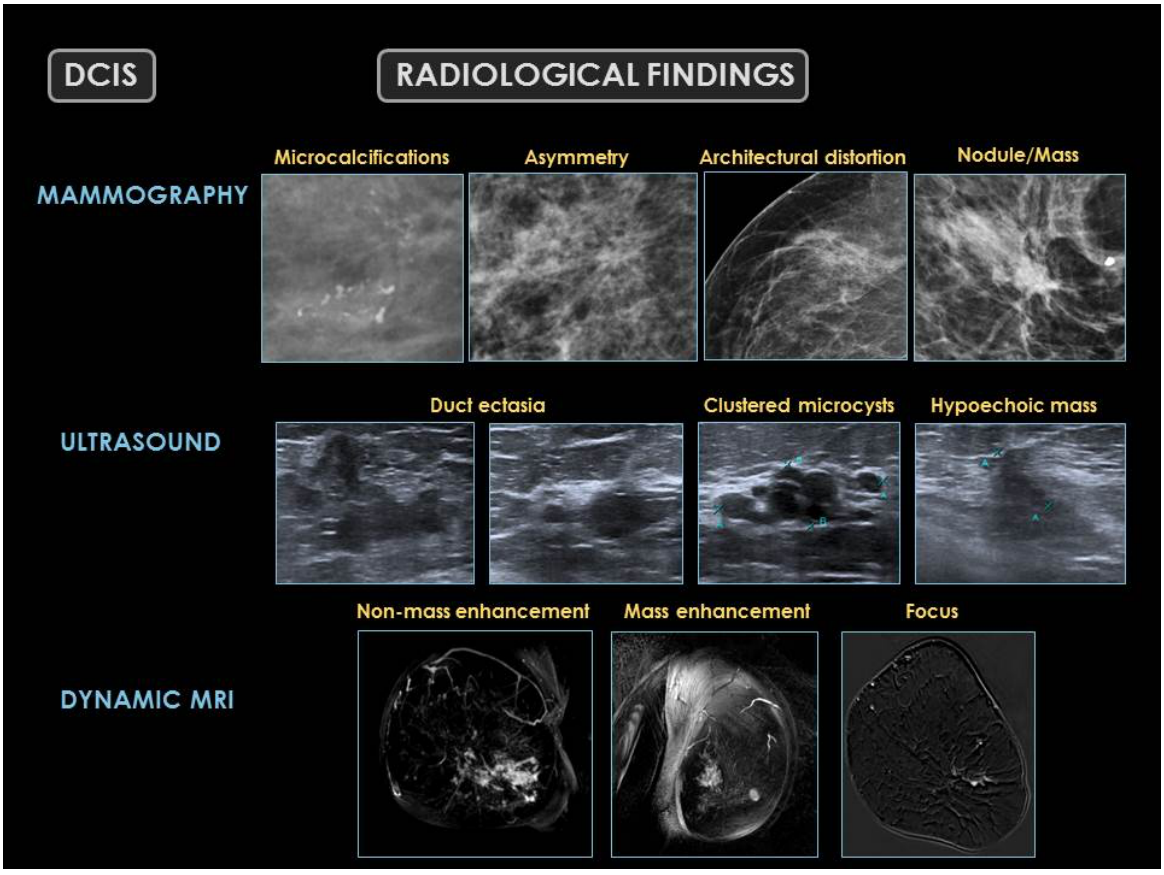

Figure 2: Radiological findings DCIS.

3.3 PATIENT PRESENTATION LCIS

Different to DCIS, classic LCIS is clinically and mammographically occult (6). Nevertheless, a careful physical examination of the breasts and regional nodes should be performed (6). LCIS will be found as an incidental finding on biopsy of the breast for other findings (6).

3.4 IMAGING STUDIES LCIS

3.4.1 MAMMOGRAPHY

With the increasing use of mammography, lobular neoplasia has been observed in association with microcalcifications in up to 40% of cases that are diagnosed by core needle biopsy (18). Microcalcifications rarely form within LCIS and it usually correlates with other benign or malignant breast lesions (18). In less than 2% of cases, classic LCIS may be associated with imaging abnormalities that result in a targeted biopsy (17).

LCIS variants, such as pleomorphic LCIS and LCIS with central necrosis, are usually detected mammographically due to associated pleomorphic calcifications, or can present as a mass lesion with or without associated calcifications (5, 18) (Fig. 3).
Bilateral mammograms should be obtained with focused diagnostic views in the area of the abnormality.

3.4.2 ULTRASOUND

Sensitivity of ultrasound is low but should be obtained if mass lesions are seen on mammography (6). Associated sonographic findings include an avascular, irregularly shaped, ill defined, hypoechoic mass with posterior shadowing (6, 19) (Fig. 4).

3.4.3 MAGNETIC RESONANCE IMAGING

Enhanced surveillance strategies that include breast MRI are commonly recommended for women at high risk, but not in a routine. It can show heterogeneous non-mass-like enhancement with persistent enhancement kinetics (6, 19) (Fig. 5).

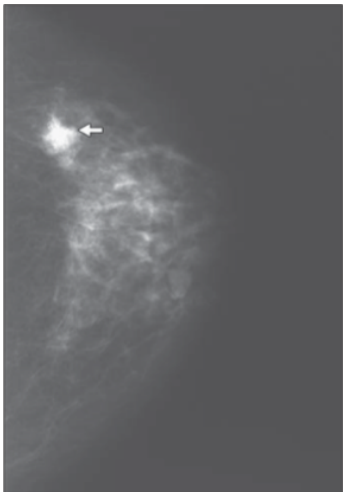

Figure 3: Mammographic mediolateral oblique view shows irregular mass (arrow) with pleomorphic calcifications in left area 1:30.

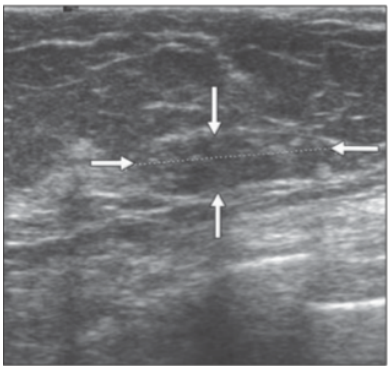

Figure 4: Ultrasound image reveals subtle, hypoechoic, ovoid-shaped, 2cm mass (arrow) containing numerous echogenic foci.

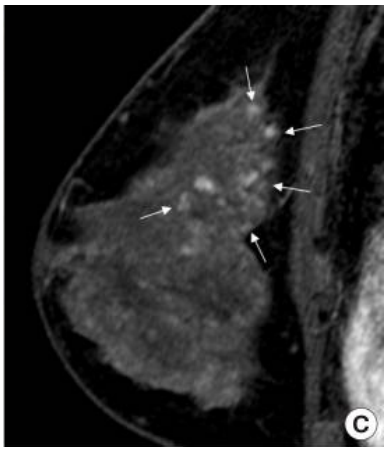

Figure 5: Early contrast-enhanced sagittal magnetic resonance image shows regional, non-mass enhancement (arrows) in the moderate background parenchymal enhancement.

4. DIAGNOSIS

4.1 PATHOLOGIC DIAGNOSTIC CRITERIA DCIS

DCIS is characterized by a proliferation of abnormal epithelial cells confined within the basement membrane (10). This confinement to the myoepithelial cell layer demarcates it from invasive breast cancer (1).

Histologically DCIS is classified by architectural growth pattern, nuclear grade and/or the presence of necrosis (10).

Based on architectural growth pattern DCIS can be classified into cribriform, micropapillary, papillary, solid, flat or clinging or comedo (10).

Variants include apocrine, cystic hypersecretory, squamous, spindle cell, signet ring cell, mucinous, small cell and some others.

Cribriform shows fenestrated proliferation with multiple, round, rigid extracellular lumens with punched out appearance (10). Neoplastic cells are frequently evenly distributed equidistant and polarized with long axis of cell perpendicular to the central lumen (10). Trabecular bars comprised of rigid rows of cells with long axes perpendicular or at least not parallel to the long axis of the bar (10). Roman bridges comprised of curvilinear trabecular bars connecting two portions of the epithelial lining (10) (Fig. 6).

Micropapillary shows papillary fronds and tufts lacking fibrovascular cores projecting into duct lumen (10). Papillae often have club shaped cell composing the micropapillae are uniform in appearance (10). Tips of fronds may fuse, forming bridges and arcades (10) (Fig.7).

Papillary fronds contain prominent fibrovascular septa projecting into duct lumen, papillary cores generally lack myoepithelial cell layer (10) (Fig. 8).

Solid shows a lumen of ducts or lobules filled with sheets of cohesive cells (10). Cells are evenly spaced especially in low or intermediate grade DCIS (10) (Fig. 9).

Flat or clinging presents with 1 - 2 layers of generally high-grade malignant cells lining a gland with a large empty lumen (10) (Fig. 10).

Comedo shows central expansile necrosis containing cellular debris, generally associated with high-grade DCIS, frequently associated with microcalcifications (10) (Fig. 11).

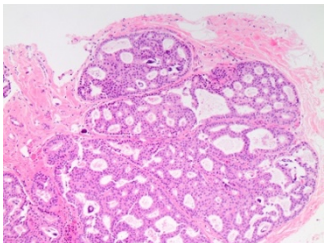

Figure 6: Low grade, cribriform. Medium power view of a terminal duct lobular unit involved by an intraductal epithelial proliferation with low grade nuclear atypia, cribriform growth pattern and microcalcifications.

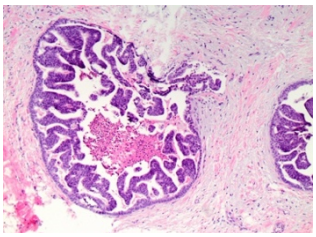

Figure 7: Intermediate grade, micropapillary. Intermediate power view of an intraductal epithelial proliferation with intermediate grade nuclear atypia, micropapillary growth pattern with focal necrosis.

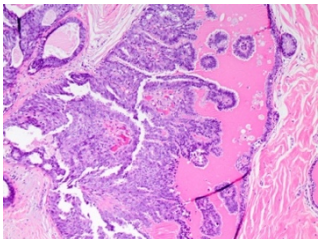

Figure 8: Intermediate grade, papillary. Intermediate power view of an intraductal epithelial proliferation with intermediate grade nuclear atypia, papillary growth pattern.

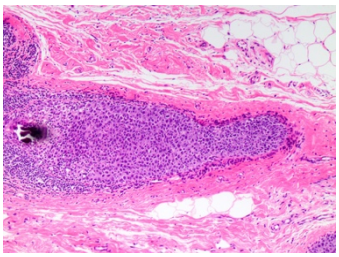

Figure 9: Intermediate grade, solid. Intermediate power view of an intraductal epithelial proliferation with intermediate grade nuclear atypia, solid growth pattern with microcalcifications.

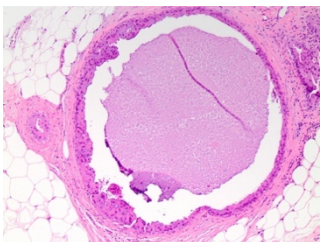

Figure 10: High grade, flat. Medium power of an intraductal epithelial proliferation with high grade nuclear atypia, flat growth pattern and central necrosis.

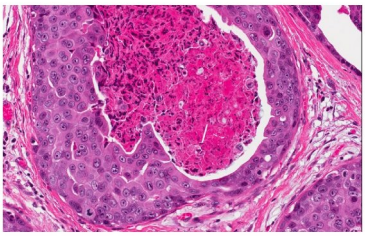

Figure 11: High-grade DCIS with central comedo-type necrosis.

There is no universally accepted grading system for DCIS but more recently endorsed classification systems stratify DCIS by nuclear grade (low, intermediate, high) (Fig.12) and presence or absence of necrosis. A consensus conference and the College of American Pathologists recommend that a pathology report should include a description of nuclear grade, presence and type of necrosis, and the architectural patterns present (20, 21).

To differentiate low, intermediate and high-grade DCIS it is needed cytological, architectural and size criteria.

Low nuclear grade DCIS is characterized by small cells with uniform size and shape and inconspicuous nucleoli (1, 10). High nuclear grade DCIS is composed of large cells with pleomorphic nuclei, prominent nucleoli, and frequent mitosis (1, 10). Intermediate nuclear grade DCIS is considered when features do not fulfil the criteria for low or high nuclear grade DCIS (1). Intermediate nuclear grade DCIS has mild to moderate changes in nuclear size and shape and a variable amount of mitosis and prominent nucleoli (1, 10). High grade tumors

represent 42 - 53% of DCIS cases and are considered a high-risk factor for recurrence and invasive breast cancer (1).

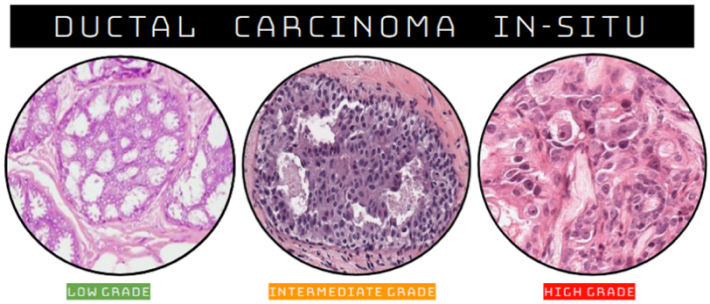

Figure 12: Nuclear grading of DCIS.

Tissue biopsy should also be evaluated for hormone receptor status, estrogen receptor (ER) and progesterone receptor (PR) and human epidermal growth factor receptor (HER-2) status. The overall ER positive expression is 69% of DCIS and is correlated with nuclear grade (strongly positive in low-grade DCIS, frequently negative in high-grade DCIS) (1).
There are specific endocrine therapies possible.

DCIS has special molecular and cytogenetic features.
Low-grade has frequent chromosomal losses at 16q and 17p and gains at 1q (1).
High-grade DCIS has losses at 8p, 11q, 13q and 14q and gains at 5p, 8q and 17q (1). High-grade DCIS has similar molecular profile as invasive breast cancer (1). Sometimes the pathologist uses this to distinct low-grade DCIS and high-grade DCIS.

Immunostains are necessary to differentiate DCIS from LCIS or invasive breast cancer. It can be performed to show myoepithelial cell retention (1). DCIS is strong membranous positive for E-cadherin and p120 and has negative stains for cytokeratin CK5/6 (1). But it shows variable or mosaic pattern of expression in high grade subtypes and usual type ductal hyperplasia (1).

4.2 PATHOLOGIC DIAGNOSTIC CRITERIA LCIS

Lobular neoplasia (LN) is an atypical proliferation of small, dyscohesive epithelial cells within the terminal duct lobular unit (TDLU), with or without pagetoid extension and encompasses both lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH) (5). The designations ALH and LCIS are used to describe the variable extent of acinar involvement, however, the distinction is quantitative and arbitrary (6) in both lesions there is a

proliferation of cytologically identical cells, but in LCIS more than a half of the acini in a TDLU are filled and expanded by neoplastic cells, whereas in ALH less than fifty percent of the acini are involved (6).

There are three major morphologic subtypes of LCIS recognized in the current WHO Classification: classic, pleomorphic and florid (3). Classic LCIS (CLCIS) is characterized by a proliferation of monomorphic, loosely cohesive type A and/or type B cells (6) (Fig. 13). Type A cells are typically small and round, with hyperchromatic nuclei and minimal cytoplasm (6) (Fig. 14). Type B cells show more variation in size and shape, have larger nuclei with vesicular chromatin and small nucleoli (6) (Fig. 15). In many cases, cytoplasmatic vacuoles can also be identified, with occasional eosinophilic globules (6). Signet ring morphology can be appreciated when cytoplasmatic vacuolation is pronounced (6). Pleomorphic LCIS (PLCIS) is composed of atypical cells, with variable sized nuclei, at least some of which are more than four times the size of a lymphocyte or equivalent to nuclei in high-grade DCIS (22) (Fig. 16). Apocrine differentiation may be seen in a subset of cases (23). Florid LCIS (FLCIS) refers to confluent mass forming CLCIS with little intervening stroma (24). Florid LCIS should have at least one of two architectural features: 1) little to no intervening stroma between markedly distended acini of involved TDLUs; 2) a minimum size cut-off of an expanded acinus or duct filling at least one high-power field (5, 24) (Fig. 17). At a minimum, an expanded acinus or duct should fill at least one high-power field. Both, PLCIS and FLCIS are more frequently associated with comedo-type necrosis and microcalcifications (17).

CLCIS is typically estrogen receptor (ER) and progesterone receptor (PR) positive, HER-2 negative (25). PLCIS may occasionally show HER-2 amplification, however it is most commonly HER-2 negative (23). The apocrine variant of PLCIS can be ER/PR negative, HER-2 positive (23).

The clonal nature of LCIS has been established through loss of heterozygosity, comparative genomic hybridization and single nucleotide polymorphism array analyses (17). ALH and CLCIS are genetically similar, demonstrating recurrent deletation of 16q and gains of 1q with a similar pattern of unbalanced chromosomal aberrations (17). Furthermore, LCIS subtypes carry the same genetic signature of 16q loss and 1q gain, with additional molecular changes, including amplification of 17q in FLCIS and deletions of 8p and 13q and gains of 8q in PLCIS, as well as overall increased genetic complexity compared to CLCIS (17). Indeed, FLCIS and PLCIS are thought to be genetically more advanced lesions, originating along the

low-grade breast neoplasia pathway and de-differentiating from CLCIS to develop a high-grade phenotype (17).
The loss of heterozygosity at 16q with resultant bi-allelic inactivation of CDH1 and impaired E-cadherin protein function is central to the pathogenesis of lobular neoplasms, both in situ and invasive (17). Approximately 60 - 80% of ILC show somatic mutations in CDH1 and the initial identification of the same CDH1 mutations in synchronous LCIS and ILC provided direct support for LCIS being a precursor lesion to ILC (17). The clonal origin for LCIS and synchronous ER positive ILC has since been demonstrated in a number of other studies (17). In addition, PLCIS and pleomorphic ILC have also been shown to share the same genetic aberrations (17). Next generations sequencing techniques have also highlighted the same combination of somatic mutations in LCIS and ILC, including mutations in CDH1, PIK3CA and CBFB (17). Although CDH1 mutations and E-cadherin dysfunction have a clear role in the pathogenesis of lobular neoplasms, germline mutations of CDH1 are infrequent in familial lobular carcinoma (17).

Immunohistochemistry for E-cadherin is frequently used to differentiate between lobular and ductal neoplasia (17). The cells of ductal proliferations typically show strong, circumferential membranous E-cadherin expression (17). In the majority of lobular neoplasm, E-cadherin shows complete absence of membranous staining (17). However, up to 10% of cases may demonstrate an aberrant pattern of expression of E-cadherin, characterized by incomplete, fragmented or beaded membranous staining, diffuse cytoplasmic staining or perinuclear dot-like pattern staining (17).

Since the accurate distinction between LN and DCIS has important clinical implications, E-cadherin staining is recommended in problematic cases (26). When E-cadherin stain is difficult to interpret, additional immunohistochemical stains can be utilized, including other members of the cadherin-catenin complex such as beta-catein and p120 (26). Demonstrating loss of membranous staining for beta-catein and cytoplasmic accumulation of p120 will lend support to a lobular phenotype (26).

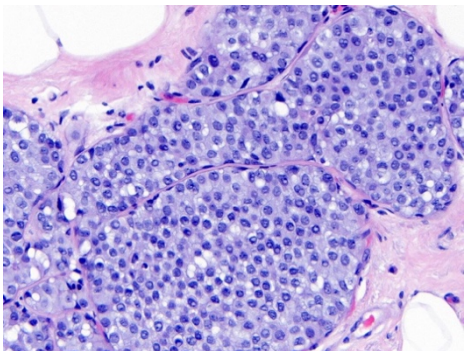

Figure 13: Classic LCIS, cell morphology.

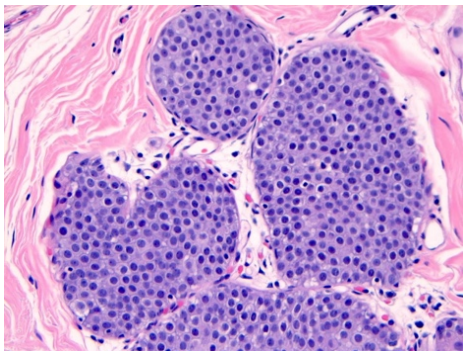

Figure 14: Type A cells.

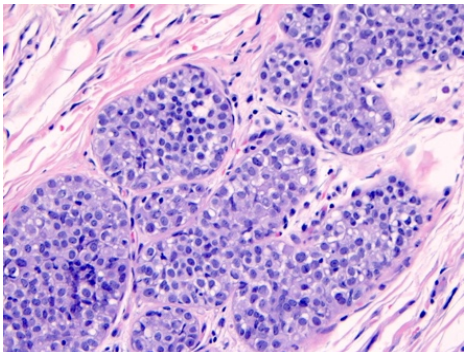

Figure 15: Type B cells.

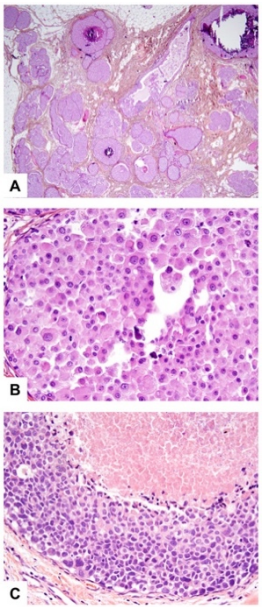

Figure 16: Pathologic features of pleomorphic lobular carcinoma in situ (PLCIS). A. Low power photomicrograph showing massive expansion of ducts and lobules by neoplastic cells, with associated comedo necrosis and calcifications (Original magnification 40x); B. High power view of PLCIS with apocrine cytology showing dyshesive cells with nuclear pleomorphism and abundant eosinophilic cytoplasm (400x); C. High power view of PLCIS with non-apocrine cytology (400x).

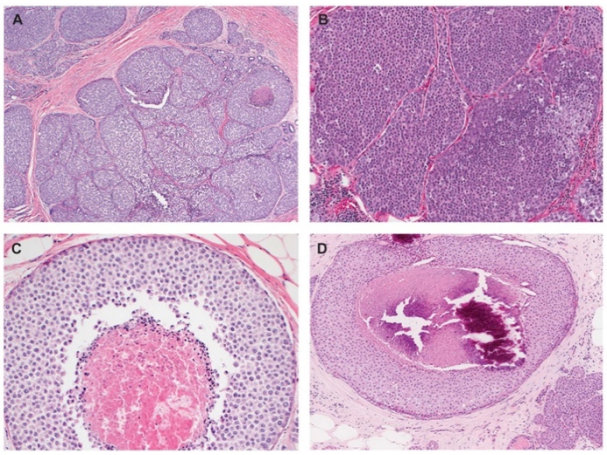

Figure 17: Florid lobular carcinoma in situ (LCIS). A. Florid LCIS has cytologic features identical to those of classic LCIS but is distinguished by marked distension of TDLUs or ducts, creating a confluent mass-like appearance at low power view. To qualify for florid subtype, an LCIS lesion should demonstrate at least one of the two architectural features depicted in B and C: (B) the spaces are expanded to a point that there is little to no intervening stroma between the markedly distended acini and ducts; (C) the expanded duct fills at least one high power field (an area equivalent to ~ 40 – 50 cells in diameter). Similar to pleomorphic LCIS, these lesions often demonstrate comedo necrosis. D. Florid LCIS with comedo necrosis and calcifications. Note the presence of classic LCIS with similar cytologic features at right lower corner, the presence of which should alert the pathologist the possibility of a LCIS subtype and not solid pattern DCIS.

5. DIAGNOSTIC EVALUATION

5.1 CORE NEEDLE BIOPSY

Percutaneous needle core biopsy of the breast is a well-established technique in the diagnostic workup of breast lesions, with a high accuracy and sensitivity (27). Based on a positive diagnosis, this procedure represents a high sensitivity (85% - 98%) and specificity close to 100% with final accuracy of 86 % to 97% (28).

Finding suspect mass lesions or microcalcifications in the mammogram women are recommended a diagnostic clarification by core needle biopsy and the number of surgical excisions can be reduced.

Using a hollow needle pieces of breast tissues from a suspicious area are taken out. The needle may be attached to a spring-loaded tool that moves the needle in and out of the tissue quickly, or it may be attached to a suction device that helps pull breast tissue into the needle (known as a vacuum-assisted core biopsy) (29). A small cylinder (core) of tissue is taken out in the needle. Several cores are often removed (29). In the case of microcalcifications in the mammogram and no palpable mass in the breast, it is necessary to guide the needle into the suspect area by ultrasound, mammogram or MRI, called stereotactic biopsy (29).

Typically, a tiny tissue marker (clip) is put into the area where the biopsy is done (29). This marker will show up on mammograms or other imaging tests so exact area can be located for further treatment (if needed) or follow up (29).

5.2 SURGICAL EXCISIONAL BIOPSY

If the histopathological result of the core needle biopsy diagnosed a classic LCIS, no other treatment follows but if results show discordance to the imaging diagnostics, or the high risk subtypes of LCIS or a DCIS, a more extensive type of biopsy, a surgical open biopsy is necessary.

An excisional biopsy removes the entire tumor or abnormal area (29). An edge (margin) of normal breast tissue around the tumor may be removed as well, depending on the reason for the biopsy. Preoperative localization by a wire marking or other localizing devices to guide surgical biopsy is necessary if it is non-palpable area (29).

The next step will depend on the pathological result.

6. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of DCIS and LCIS can be difficult in some cases and also includes other intraductal epithelial cell proliferations and lobular in situ neoplasia.

There clearly is an overlap in the distribution with the ductal-lobular system; DCIS can involve identifiable lobules and LCIS can involve ducts (30).

Classic LCIS versus low-grade DCIS

CLCIS and low-grade DCIS of solid type can appear morphological similar (17).

The identification of cribriform areas and cellular cohesion is more in keeping with a ductal lesion (17).

Immunohistochemistry can be helpful by demonstrating lost or aberrant membranous E-cadherin staining in LCIS (17) (Fig. 18, 19, 20, 21).

Pleomorphic LCIS versus high-grade DCIS

The distinction between PLCIS and high-grade DCIS may be difficult, given that both lesions comprise large atypical cells with frequent comedo type necrosis and calcification (17, 30).

Both lesions can show aberrant E-cadherin staining on immunohistochemistry (5, 6, 10, 17).

PLCIS should be suspected when the proliferation comprises dyscohesive cells with intracytoplasmic vacuoles and eosinophilic globules (17). Surrounding CLIS may also be a clue to the lobular nature of the lesion (17, 30) (Fig. 19, 20, 21).

Florid LCIS/LCIS with comedo necrosis versus DCIS with comedo necrosis

Florid type is a kind of morphological variation of LCIS (31). Florid LCIS has the same cytological features as LCIS, often associated with comedo-type necrosis (31).

Florid LCIS can be associated with mammographic and histological calcification and/or comedo necrosis (31). Therefore, it can histological mimic solid low and intermediate DCIS (32).

Recognition of characteristic cytologic features of LCIS (dyshesion and intracytoplasmatic vacuoles) and an immunostain for E-cadherin leads to the correct diagnosis (6) (Fig. 19, 20, 21).

Mixed lesions

In some cases, both LCIS and DCIS, can occur in the same TDLU (17). Morphological features such as loss of cellular cohesion as well as absent/aberrant E-cadherin staining can be used to identify the LCIS component (17).

Feature	LCIS variants	DCIS
Loss of cohesion	Yes	No
Intracytoplasmic vacuoles	More common	Less common
Pagetoid ductal involvement	More common	Less common
Associated classical LCIS	More common	Less common
Microacini	Absent	Present
Polarization of cells at periphery	Absent	Present

Figure 18: Histologic distinction between LCIS variants and DCIS.

	Normal epithelium	LCIS and ILC	DCIS and IDC
E-cadherin	Membrane staining	Absence of membrane staining	Membrane staining
p120 catenin	Membrane staining	Cytoplasmic staining	Membrane staining
β-catenin	Membrane staining	Absence of membrane staining	Membrane staining

Figure 19: Expected expression of E-cadherin, p120 catenin.

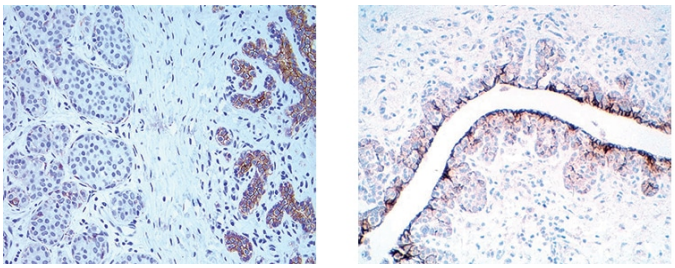
Figure 20: LCIS: Loss of E-cadherin expression.

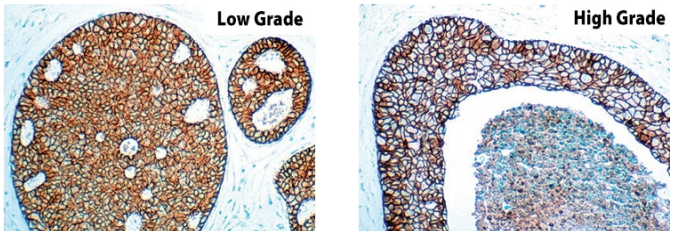

Figure 21: DCIS: E-cadherin positive.

Flat epithelial Atypia

Flat epithelial Atypia is a proliferation of 1-5 cell layers composed of cells with low-grade nuclear atypia but with architectural features not meeting the criteria for DCIS, ADH and ALH (32).

Usual ductal Hyperplasia

In UDH, there is an overgrowth of cell lining the ducts in the breast, but cells look very close to normal (26). The Heterogeneity can mimic intermediate grade DCIS (10). It shows variable or mosaic pattern of expression of CK5/6 and CK5 and Estrogen receptor is diffusely positive (10) (Fig. 22).

Atypical ductal Hyperplasia

Atypical ductal Hyperplasia is an intraductal clonal epithelial cell proliferation (34). ADH and low-grade DCIS have the same atypical histological features (34). ADH is differentiated from low-grade DCIS by size or volume; if the atypical cells involve =<2mm, =2 spaces, or a portion of a duct a diagnosis of ADH is made (34). Although size is helpful there is no universally accepted size criterion for ADH (34).

ADH has similar architectural features to DCIS, such as arcades, rigid bridges, bars of uniform thickness, a solid growth pattern, and micro papillae (34).

Patients with a diagnosis of ADH on a core biopsy sometimes have worse lesions (DCIS or Invasive carcinoma) on surgical excision (34). It is important to know the type of specimen in which the ADH is identified because the lesions management depends on it (34) (Fig. 22).

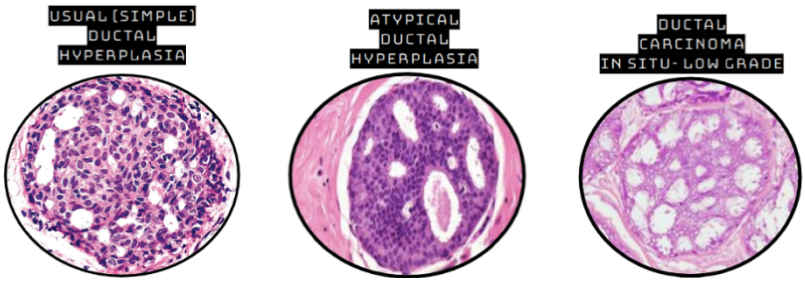

Figure 22: Intraductal Proliferations.

Microinvasive Carcinoma of the DCIS

Currently, the American Joint Committee on Cancer (AJCC) staging manual defines microinvasive carcinoma as "the extension of cancer cells beyond the basement membrane into adjacent tissue with no focus more than 0.1 cm in greatest dimension," and it formally includes microinvasive carcinoma in the T staging system, where this disease is categorized as T1mi (36).

Microinvasion is usually present in high-grade, comedo-type DCIS and is less likely to be found in other types of DCIS or in LCIS (36).

Immunohistochemistry can assist in the identification of a myoepithelial layer around islands of such atypical epithelial cells (36).

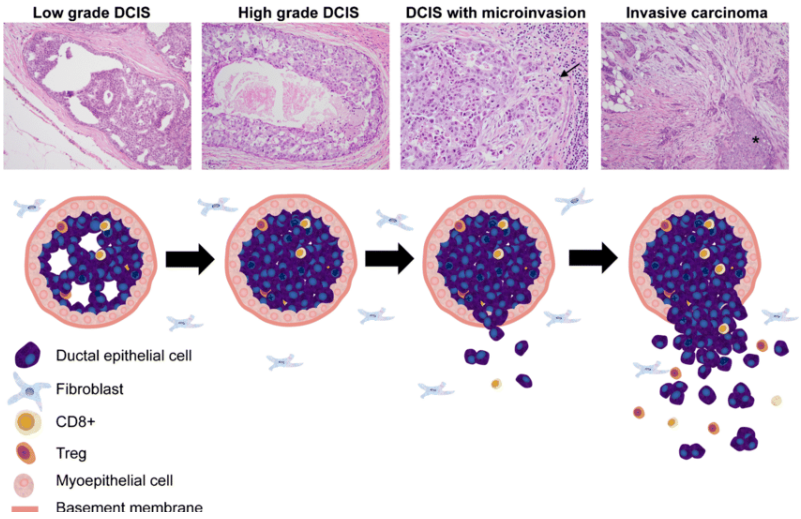

Figure 23: Progression of ductal carcinoma in situ to invasive carcinoma from a histopathologic perspective. Representative micrographs and schematic representation of progressive stages of breast cancer including in situ carcinoma, microinvasive carcinoma and invasive carcinoma.

Atypical lobular Hyperplasia

ALH is characterized by an intraductal over-proliferative epithelial population within the acini of terminal duct lobular units (37). These proliferations consist of small, round uniform cells

that do not overlap, appear more dyshesive, and have increased nuclear to cytoplasmic ratio (37). Nuclear atypia should be minimal (37). Loss of E-cadherin staining is characteristic for ALH and is also seen in more advanced lesions such as lobular carcinoma in situ or invasive lobular carcinoma (37). The distinction between ALH and lobular carcinoma in situ is that with ALH, there should be less than 50% involvement of the acini in the TDLU (37, 38).

7. POSTDIAGNOSTIC EVALUATION

7.1 TNM STAGING DCIS

The American Joint Committee on Cancer (AJCC) defines ductal carcinoma in situ as Tis (DCIS) (39).

Tis refers to carcinoma in situ. It is a preinvasive breast cancer and the cells are in the breast ducts and have not started to spread into surrounding breast tissue (6).

DCIS is described as stage 0 (29).

Although DCIS is always stage 0, the tumor can be any size and may be located within several milk ducts inside your breast.

The final pathology report should include the following features:

Tumor size
Distance to margins
Nuclear grade
Presence and type of necrosis
Immunostains like ER, PR, E-cadherin, p120 catenin

7.2 TNM STAGING LCIS

In the 8th edition of the American Joint Committee on Cancer (AJCC) staging system, LCIS has been removed from the staging classification system and is no longer included in the pathologic tumor in situ (pTis) category (5) because it is considered a risk factor, not a malignancy. Reporting on size or margin status is not necessary (5).

The latest edition of the WHO Blue Book for breast tumors refers to the TNM AJCC staging and also recognises that PLCIS should be treated by surgical excision as per the recommendations of several international guidelines (3).

7.3 RISK ASSESSMENT FOR HEREDITARY BREAST CANCER

About 5% to 10% of breast cancer cases are thought to be hereditary, meaning that they result directly from gene changes (mutations) passed on from a parent (40).

BRCA1 and BRCA2: The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 gene (40). In normal cells, these genes help make proteins that repair damaged DNA (40). Mutated versions of these genes can lead to abnormal cell growth, which can lead to cancer (40).

- If patients have inherited a mutated copy of either gene from a parent, they have a higher risk of breast cancer (40).
- On average, a woman with a *BRCA1* or *BRCA2* gene mutation has up to a 7 in 10 chance of getting breast cancer by age 80 (40). This risk is also affected by how many other family members have had breast cancer (40). (It goes up if more family members are affected.) (40).
- Women with one of these mutations are more likely to be diagnosed with breast cancer at a younger age, as well as to have cancer in both breasts (40).
- Women with one of these gene changes also have a higher risk of developing ovarian cancer and some other cancers (40). (Men who inherit one of these gene changes also have a higher risk of breast and some other cancers.) (40).
- In the United States, *BRCA* mutations are more common in Jewish people of Ashkenazi (Eastern Europe) origin than in other racial and ethnic groups, but anyone can have them (40).

Other genes: Other genes mutations, ATM, PALB2, TP53, CHEK2, CDH1 can also lead to inherited breast cancers (40). These gene mutations are much less common, and most of them do not increase the risk of breast cancer as much as the *BRCA* genes (40).

Genetic counseling and testing: Genetic testing can be done to look for inherited mutations in the *BRCA1* and *BRCA2* genes (or less commonly in genes such as *PTEN*, *TP53*, or others mentioned above) (40). This might be an option for some women who have been diagnosed with breast cancer, as well as for certain women with factors that put them at higher risk for breast cancer like DCIS or LCIS, such as a strong family history (40).

While genetic testing can be helpful in some cases, not every woman needs to be tested, and the pros and cons need to be considered carefully (40).

There are different risk assessment tools like Gail, Tyrer-Cuzik or BRCAPRO models. But these tools cannot accurately estimate breast cancer risk but can be used as a decision-making aid for women carrying a BRCA1 or BRCA2 mutation or women with a previous history of invasive or in situ breast cancer (41).

If there is a hereditary breast cancer risk and a lobular neoplasia or DCIS in the own history, decision of the treatment must be discussed in an interdisciplinary panel and tumorboard (Fig. 24).

TABLE 1

Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer: Clinical Summary of the USPSTF Recommendation

Population	Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations	Women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations
Recommendation	Assess with an appropriate brief familial risk assessment tool. Grade: B	Do not perform routine risk assessment, genetic counseling, or genetic testing. Grade: D
Risk assessment	Patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer or ancestry associated with harmful *BRCA1/2* mutations should be assessed using a familial risk assessment tool. The USPSTF found adequate evidence that these tools are accurate in identifying women with increased likelihood of *BRCA1/2* mutations. Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), and brief versions of BRCAPRO. These tools should be used to guide referrals to genetic counseling.	
Genetic counseling	Genetic counseling about *BRCA1/2* mutation testing should be done by trained health professionals, including suitably trained primary care providers. The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful *BRCA1/2* mutations. It also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options.	
Genetic testing	Tests for *BRCA1/2* mutations are highly sensitive and specific for known mutations. Testing for *BRCA1/2* mutations should be done when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to see a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision making.	
Treatment and interventions	In general, women with harmful *BRCA1/2* mutations are managed with a variety of interventions to lower future cancer risk. This includes intensive screening, risk-reducing medications, and risk-reducing mastectomy and salpingo-oophorectomy.	
Other relevant USPSTF recommendations	The USPSTF recommends that clinicians offer to prescribe risk-reducing medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer and at low risk for adverse medication effects. It recommends against the routine use of medications for risk reduction of primary breast cancer in women not at increased risk for breast cancer. The USPSTF recommends against screening for ovarian cancer in women. This recommendation does not apply to women with known genetic mutations that increase their risk for ovarian cancer (e.g., *BRCA1/2* mutations). The USPSTF found insufficient evidence to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic women for the early detection and treatment of a range of gynecologic conditions.	

Note: For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, go to https://www.uspreventiveservicestaskforce.org/.

USPSTF = U.S. Preventive Services Task Force.

Figure 24: Risk assessment, genetic counselling and genetic testing for BRCA-related cancer: clinical summary of the USPSTF recommendation.
USPSTF = U.S. Preventive Service Task Force

8. TREATMENT

8.1 TREATMENT DCIS

Treatment for DCIS include two options, breast-conserving surgery followed by radiation and simple mastectomy. For both options there is an equivalent long-term outcome (1, 2). According to the guidelines of National Comprehensive Centre Network (NCCN) and Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) breast-conserving surgery followed by radiation is recommended (42, 43).

Breast-conserving surgery or lumpectomy

The first step is pre-surgical localization of the lesion as many of these lesions are non-palpable (1). This can be done by wire localization immediately pre-procedure or wireless radioactive seed, which can be placed in the days prior to surgery (1).
The lesion should be excised with a 2mm free margin on final pathology (1). Once removed, the specimen should be tagged and oriented in three-dimensional space using ink or marking suture (1). After X-ray confirmation of the biopsy, a clip should be placed to mark the location for radiation planning (1).

Mastectomy

Mastectomy is recommended in patients with multicentric/multifocal disease, an extensive disease where surgeon could not reach a good cosmesis or after re-resection there are positive margin, or patient who cannot receive radiation therapy (1, 10).
Mastectomy is curative in 98% of patients with DCIS (44) (1). Axillary lymph node involvement in DCIS is rare; thus, sentinel lymph node (SLN) biopsy is not indicated during breast-conserving surgery, only patients who have DCIS size > 5 cm or at high risk microinvasive carcinoma (10).

Radiation

Radiation is recommended after breast-conserving operation (BCO).

The NSABP B17 trial demonstrated that in patients who underwent BCO and were followed with radiation, there is a 50 to 60% reduction in local recurrence with surgical excision and radiation therapy compared to surgical excision alone (1).
Typically, patients will undergo whole breast normofractionated radiation with a total dose of 50 to 60 Gy (1). Patients will have radiation treatment 5 days a week with 2 Gy fractions of radiation for a total of 5 weeks (1).
Omission of radiotherapy may be considered if DCIS is small, low grade and has clear negative margins (10) or high age and comorbidities.

Endocrine Therapy

Endocrine therapy is an option if the DCIS specimen express estrogen (ER) and/or progesterone receptors (PR) (1). Tamoxifen has been demonstrated to prevent breast cancer recurrences in women with DCIS (1, 2). In the NSABP B 24 trials, women with ER-positive DCIS treated with tamoxifen had significant decreases in any subsequent breast cancer events when given over five years post-diagnosis. This risk reduction is applied to both the ipsilateral and contralateral breast (45).
Aromatase inhibitor like Anastrozole shows a comparable effectiveness in the adjuvant situation in postmenopausal patients.
Because of the side effects and no evidence of survival advantage, endocrine therapy is not generally recommended.

8.2 TREATMENT LCIS
There are three main approaches to treatment:

Active surveillance
Preventive medication to reduce the risk of invasive breast cancer
Surgery

Active surveillance and chemoprevention are management options for classic LCIS (5).
Different studies could show acceptably low upgrade rates (1% - 4,4%) at surgical excision (6).
So routine excision is not indicated for patients with classic LCIS or ALH on core needle biopsy (5). Only with discordant imaging findings surgical excision is recommended. As

specified in the 2016 consensus guidelines by the American Society of Breast Surgeons, “we no longer advocate *routine* excision of ALH or LCIS when the radiological and pathological diagnoses are concordant, and no other lesions requiring excision are present” (47).
After active surveillance the NCCN guidelines recommend clinical breast exam every 6 - 12 months in conjunction with an annual mammogram (42).
The American Society of Clinical Oncology Clinical Practice guidelines recommend that the use of chemoprevention should be discussed as an option to reduce the risk of breast cancer in high-risk patients.
Results of randomized controlled clinical trials support the use of tamoxifen or aromatase inhibitors for risk reduction among women at increased risk of breast cancer. Tamoxifen reduced the risk of invasive breast cancer by 49% (see Chapter Chemoprevention).

LCIS variants (pleomorphic LCIS or LCIS with necrosis/florid LCIS) diagnosed on core biopsy requires surgical excision (5). The reported upgrade rates were 25% - 30% (5).
According to the NCCN guidelines (42), “Some variants of LCIS (pleomorphic LCIS) may have a similar biological behavior to that of DCIS (42). Clinicians may consider complete excision with negative margins for pleomorphic LCIS, but this may lead to high mastectomy rate without proven clinical benefit (42). There are no data to support using radiotherapy in this setting” (42).
In a resection specimen, the margin status of classic LCIS is not reported, but it should be reported for LCIS with variant and/or pleomorphic morphology (5).
Without negative margin status mastectomy could be necessary in high-risk patients (6).
In patients who are *BRCA1* or *BRCA2* gene mutation carriers, prophylactic mastectomy is the most effective single intervention for overall survival (6).

8.3 FOLLOW-UP CARE

According to ASCO-ACS recommendations 2016, NCCN 2021, ESMO 2019 and S3-guidelines 2017 the follow-up care for non invasive breast cancer is the same for DCIS and LCIS (Fig. 25).
It contains monthly self- examination, for the first 5 years after primary therapy. History, physical examination and counseling is recommended every 6 months and annual mammography and additional sonography, breast MRI only if the conventional imaging is inconclusive.

Except, high-risk patients with hereditary breast cancer or genetic mutations, a multimodal intensive surveillance program with semi-annually clinical breast examination and sonography, annually mammogram and breast MRI is recommended.

Follow-Up Care for invasive / non-invasive Breast Cancer

Recommendations for asymptomatic pts.
(mod. according to ASCO-ACS recommendations 2016, NCCN 2021, ESMO 2019 and S3-guidelines 2017)

Clinical follow-up		Follow-up*		Screening/ Follow-up
Years after primary therapy		1 2 3	4 5	> 5
History, physical examination, counseling		every 3 months DCIS every 6 months	every 6 months	inv.: every 12 months
Self-examination		monthly		
Imaging modalities and biochemistry		indicated only if complaints, clinical findings, or suspicion of recurrence Monitoring of side effects of therapy		
Mammo-graphy and additional sonography	BCT**	both sides: every 12 months		
	Mastectomy	contralateral every 12 months		
Echocardiography		6,12,24 months and yearly up to 5 years after completion of cardiotoxic therapy, after 5th year, every 5 years and if patient is symptomatic.		

* Continued follow-up visits if still on adjuvant treatment
** In pts after breast-conserving therapy (BCT): First mammography 1 year after initial mammography or at least 6 months after completion of radiotherapy

Figure 25: Follow-Up for invasive/non-invasive breast cancer (AGO Guidelines Version 2022).

9. CHEMOPREVENTION

Chemoprevention with selective estrogen receptor modulators (SERMs) like tamoxifen or raloxifene and aromatase inhibitors (AI) like exemestane or anastrozole can reduce breast cancer risk (48) (Fig. 26). This knowledge is based on multiple international trials (NSABP-B24, NSABP-B35, IBIS-I und IBIS-II, STAR). A SERM, can reduce invasive breast cancer incidence in high-risk women by 30 - 50% compared to placebo when taken for five years (49). Another SERM, raloxifene, has been shown to have similar effects in postmenopausal women (49). Based upon the results of these trials, the U.S. Food and Drug Administration (FDA) approved tamoxifen for breast cancer risk reduction in 1998 and raloxifene in 2007 (49).

In 2011 and 2014, the aromatase inhibitors (AI), exemestane and anastrozole, were demonstrated to reduce invasive breast cancer incidence by 50 - 65% compared to placebo among high-risk postmenopausal women (50, 51).

Based upon this evidence, the U.S. Preventive Services Task Force (USPSTF), American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the Arbeitsgemeinschaft gynäkologischer Onkologie (AGO) distributed guidelines on breast cancer chemoprevention (42, 43, 52). High-risk premenopausal and postmenopausal

women, defined as those with a 5-year Gail risk score of ≥1.67% or those with LCIS, may take tamoxifen for five years to reduce breast cancer risk (49). Tamoxifen is most likely to benefit younger women (age 35 - 50 years), those who have undergone a hysterectomy, and those at higher risk for breast cancer (49). Women who have gone through menopause also have the option of raloxifene, anastrozole, or exemestane to reduce breast cancer risk (49).

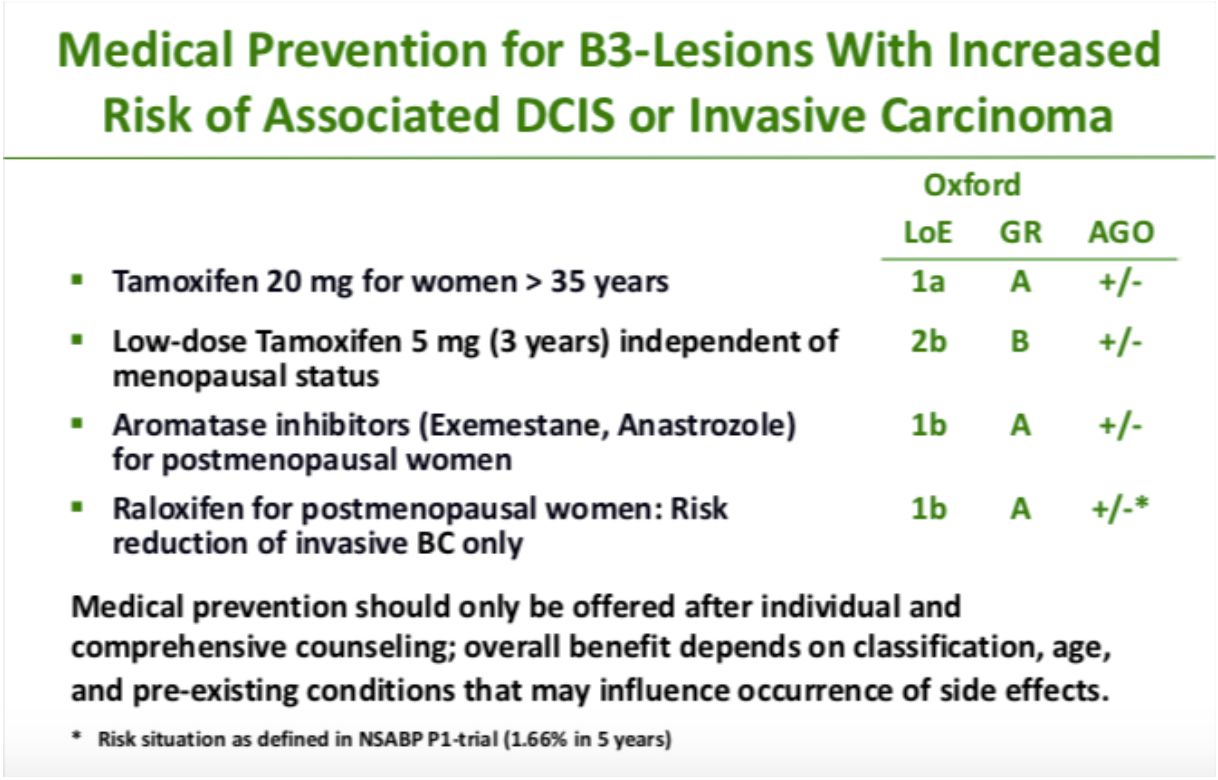

Figure 26: Chemoprevention recommendation for low-dose Tamoxifen therapy in premalignant DCIS/ LCIS (AGO Guidelines Version 2022).

A good risk and benefit assessment is required and the prescription must be well balanced. All the SERMs and AIs will have different side effects, tamoxifen use has an increased risk for endometrial cancer, cataract, both SERMs are associated with an increased risk of venous thromboembolism and pulmonary embolism, taking AIs may increase the risk of osteoporosis and thus of bone fractures.

De Censi et al. presented on December 6, 2018 on San Antonio Breast Cancer Symposium that in an Italian 500 patient study, TAM-01, low dose tamoxifen (5mg/d) (so-called Baby Tam) for 3 years instead of 20mg/d for 5 years, may be an effective chemopreventive strategy, with good tolerability in this population (53). In women with ductal carcinoma in situ and other forms of intraepithelial neoplasia, low-dose tamoxifen (5 mg/d) given for 3 years reduced the risk of breast cancer development by 52%. Side effects in the tamoxifen arm were no higher than in the placebo arm (53).

Currently, de Censi et al. updated the results from the phase 3 trial TAM-01 at San Antonio Breast Cancer Symposium, December 6-10, 2022, (Abstract GS4-08) (Fig. 27). The results could be confirmed, there is a significant lower risk of ipsilateral (52%) or contralateral (76%) recurrence events. De Censi noticed, that "Baby Tam" can be the standard of care in women with high-risk lesions, it is very effective and nontoxic and allows a de-escalation at DCIS/LCIS (Fig. 27).

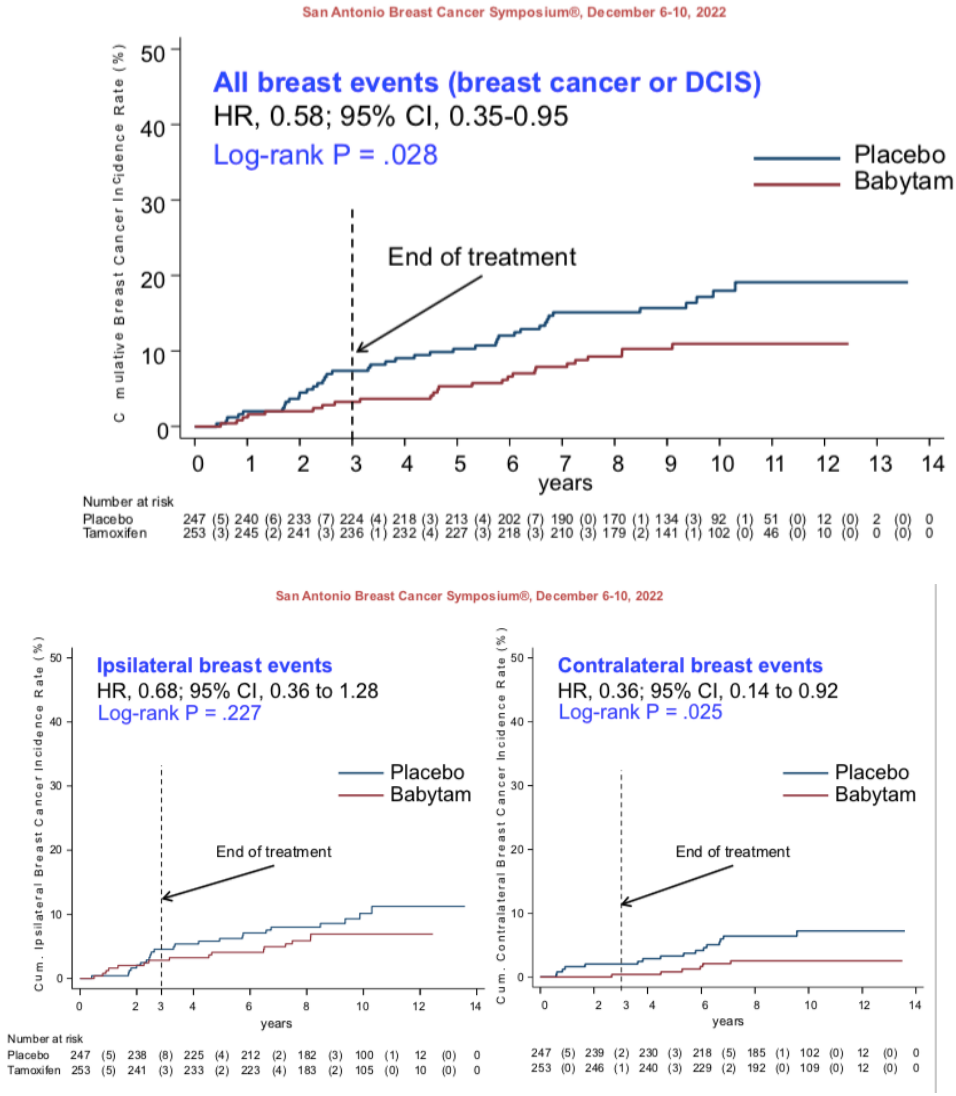

Figure 27: 10-year results of a phase 3 trial of low-dose tamoxifen in non-invasive breast cancer.

The question must be discussed, "When does the benefit of breast cancer risk reduction outweigh the risk of side effects and toxicities from the drug's use?"

The treatment arm with low dose tamoxifen were shown to have only 1 additional hot flash per day vs placebo.

Individualized treatment recommendations have to be discussed under consideration of the risks and benefits.

10. PROGNOSIS

The treated DCIS and LCIS have a favorable prognosis.

DCIS:
The risk is 10 times higher for women to develop ipsilateral invasive breast if they are diagnosed with DCIS and don't get appropriate treatment (10).
36 - 53% of low-grade DCIS lesions progress to invasive lesions if untreated (10).
As most clinically detected high-grade DCIS is excised surgically therefore the risk of progression of untreated high-grade DCIS to invasive carcinoma is not well characterized (2).

Despite the excellent prognosis of patients with treated DCIS, there is still an increased breast cancer mortality. In a recent 2020 study published in JAMA Oncology of over 100,000 patients diagnosed with DCIS, the overall death rate from breast cancer at 20 years after diagnosis was 3.3%, a rate treble that of the general population (2). That rate was the same with either breast conservation therapy or mastectomy (2). Interestingly, the same study found the prevention of invasive in-breast recurrence with either radiotherapy or mastectomy did not reduce breast cancer-specific mortality (2).

There is a variation in the time interval to the development of recurrence. Low-grade DCIS has a longer interval (>15 years) and high-grade DCIS has a shorter interval (<5 years) (11).
There was a 15-year total local recurrence rate of 40% with 28% recurring as invasive disease seen in a long-term outcome meta-analysis study of DCIS (10).
The most important clinical pathologic predictors associated with local recurrence and prognosis are positive surgical margins, high nuclear grade, large lesion size, comedo necrosis and young age (<45 years) (10) (Fig. 28).

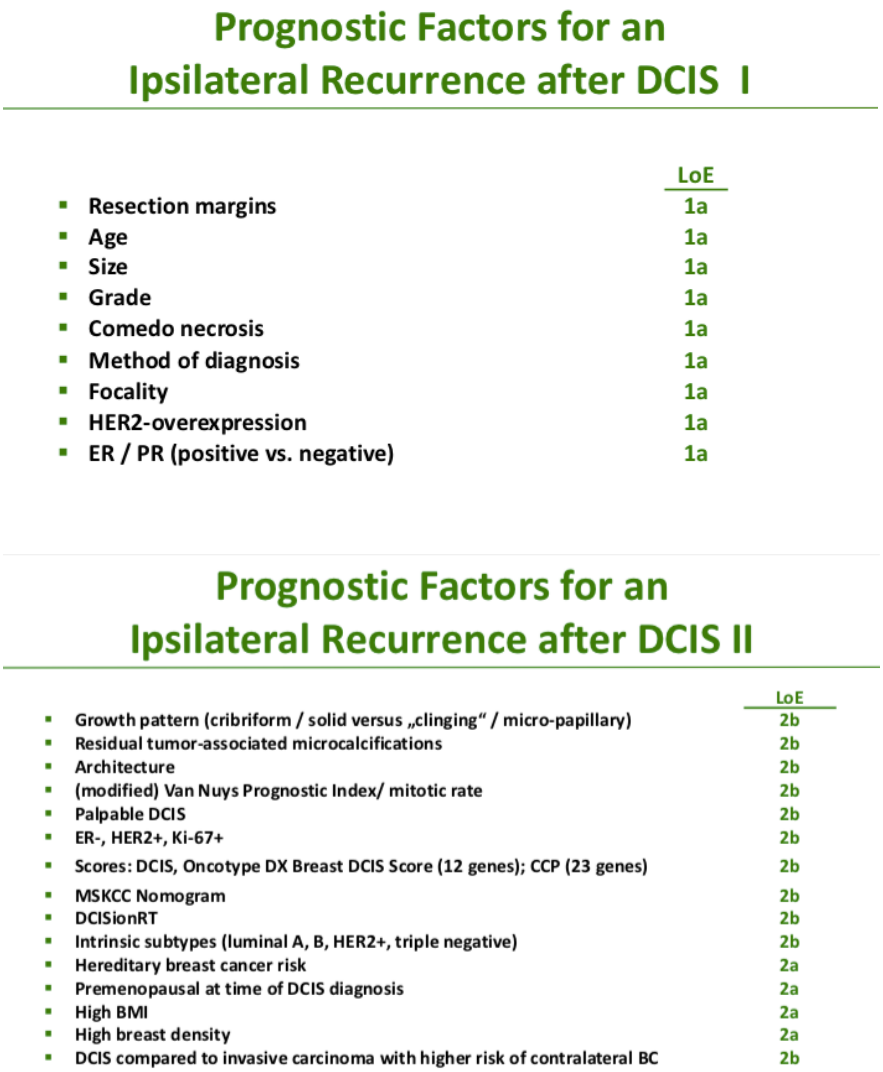

Figure 28: Prognostic Factors for local recurrence after DCIS (AGO Guidelines Version 2022).

One of predictive and prognostic biomarker for DCIS is the estrogen receptor (1). The estrogen receptor is currently the only immunohistochemical biomarker recommended for routine clinical use; progesterone which is considered as optional (11). The estrogen receptor determines the potential benefit of endocrine therapies. The Estrogen receptor negative status correlates with ipsilateral recurrence risk.

Another predictive and prognostic biomarker is the Oncotype DX DCIS score which is a Multigene expression assay for DCIS patients that generates individualized estimates of 10-year risk of any local recurrence (LR) (DCIS or invasive BC) and invasive LR in patients with DCIS treated with breast conserving surgery alone (10, 54). The Oncotype DX DCIS is a scoring system that categorizes cancers as low, intermediate or high risk (55). A large population-based study presented at the 2014 San Antonio Breast Cancer Symposium

validated the Oncotype DX DCIS in a diverse population of women with DCIS (55). The Oncotype is expressed in variables from 0 to 100. A DCIS Score of less than 39 indicates a low risk for tumor recurrence, a DCIS Score of 39 to 54 indicates an intermediate risk for tumor recurrence and a DCIS Score of 55 or higher indicates a high risk for tumor recurrence (54).
Rakovitch showed, if DCIS Score was used retrospectively, the 10-year risk of local tumor recurrence was estimated at 13% of low-risk patients, 28% for intermediate risk patients and 33% for high-risk patients (54).

Novel biomarkers that are not used in routine clinical practice are in recent studies correlated presence of associated tumor infiltrating lymphocytes (TIL) in periductal stroma and TIL immune phenotype to high-risk features and Oncotype DX Breast DCIS Score (10). A high Ki67 proliferation index has reported to correlate with increased recurrence risk. HER2 (epidermal growth factor receptor family member 2) more frequently expressed (~ 40%) in DCIS than invasive carcinoma and reported to correlate with increased recurrence risk (10). Several novel biomarkers such as COX-2, FOXA1, SIAH2 and p16 have been evaluated in DCIS with regard to radiotherapy benefit and recurrence risk (10).

A nomogram for predicting recurrence risk after breast conserving surgery based on clinical, pathologic and treatment variables has shown utility in providing individualized estimates of recurrence risk (10).

Silverstein et al. published 1996 the Van Nuys Prognostic Index (VNPI) (Fig. 29) to classify patients with DCIS to guide decisions on the best treatment option (56).
The modified index from 2003 uses patient age, tumor size, tumor growth patterns (histological grade) and the amount of healthy tissue surrounding the tumor after removal (resection margin width) to predict the risk of cancer returning (56).
After adding together the score from each of these factors, patients are classified into three categories (56) (Fig. 29).

- low-risk (total VNPI score of 4-6) breast conserving surgery (BCS) without radiotherapy is recommended
- intermediate-risk (total VNPI score of 7-9) BCS with radiotherapy is recommended
- high-risk (total VNPI score of 10-12) mastectomy is recommended

Feature	Score 1	Score 2	Score 3
Size (mm)	≤15	16–40	>40
Margins (mm)	≥10	1–9	<1
Grade and necrosis	Low or intermediate without necrosis	Low or intermediate with necrosis	High grade with/without necrosis
Age (years)	>60	40–60	<40
	Low score (4–6)	**Intermediate (7–9)**	**High (10–12)**
% patients	32.6%	56.7%	10.8%
Treatment recommendation	Wide-local excision (WLE)	WLE + radiotherapy (RT)	Mastectomy
10 year recurrence-free survival[a]	97%	73%	34%
10 year breast cancer-specific survival	100%	98%	98%

[a]After WLE ± RT, mastectomy excluded

Figure 29: Van Nuys Prognostic Index and recommendations for treatment (56).

The VNPI is not an optimal tool for the choice of DCIS patients (57). It can be helpful only in some clinically difficult cases as one of the many methods of assessing the risk of DCIS recurrence (57). The ranges which were given a specific numerical value are not consistent with the current research findings and recommendations of scientific societies (57).

LCIS:

LCIS is both a risk factor for and a nonobligate precursor of invasive breast carcinoma (5). Most of the risk relates to subsequent invasive ductal carcinoma rather than to invasive lobular carcinoma.

The cumulative risk of subsequent invasive breast carcinoma was 8% after 5 years, 15% after 10 years, 27% after 15 years, 35% after 20 years, and over 50% after 23 years (58). The cumulative risk of contralateral breast cancer was 10% after 10 years, 15% after 15 years, and 25% after 20 years (58).

The annual incidence of breast carcinoma in women with LCIS was 2%. The subsequent breast carcinoma included DCIS (35%), IDC (29%), ILC (27%), and other types of invasive carcinoma (9%) (5). 85% of all LCIS are mulitcentric and 67% are bilateral (5).

The relative risk of subsequent breast carcinoma in patients with LCIS is 9-10 times greater than that in the general population (8, 9). The relative risk of invasive breast carcinoma after diagnosis ALH is 3-5 times that of general population (9), approximately one-half that of LCIS (9).

Presence of LCIS at (or close to) the margin of resection is not associated with increased local recurrence (6).

The heterogeneity of LCIS makes it so difficult to find general therapy recommendation.
The three subtypes of LCIS have different risks of developing invasive breast cancer.

11. DISCUSSION

DCIS and LCIS are two types of Carcinoma in situ.
While DCIS is considered a pre-cancer, LCIS is only a risk factor for developing an DCIS, an invasive ductal carcinoma or an invasive lobular carcinoma.
Since introduction of the screening of mammograms for women at 50 years, diagnosis of DCIS and LCIS occur frequently.
DCIS and LCIS are histomorphological very heterogeneous. Depending on the sub-groups it shows a different risk potential.
For the treating physicians, this is a great challenge of therapy management.
On one side the pathologist must be absolutely sure in his histopathological classification. It is not always easy to differentiate LCIS from DCIS. Immunohistochemical methods like the determination of E-cadherin staining are used. To clarify diagnosis, sometimes a second opinion is necessary.
Only when all criteria are met, clinicians, oncologists, radiologists, surgeons and psychologists can decide an individual therapy management with all benefits and risks for the patient. While the familial and genetic profile such as the wish of the patient are taken into account.
According the guidelines of AGO or NCCN for classic LCIS an active surveillance is recommended, in difference to the non-classic LCIS or DCIS, that can vary from conserving operation to radical surgery with or without radiation.
Chemoprevention respectively endocrine therapy is individually discussed at high-risk patients as well as LCIS as well as DCIS (see data of the trial TAM-01).
Especially the subgroup of low-risk DCIS is a challenge for the therapy decision.
Nobody can predict if and when a malignant tumor will develop from a newly discovered DCIS.
We still know too little about the origin of carcinoma. Knowledge on the underlying mechanism of progression from DCIS to IBC is still limited. There are different models (Fig. 30).

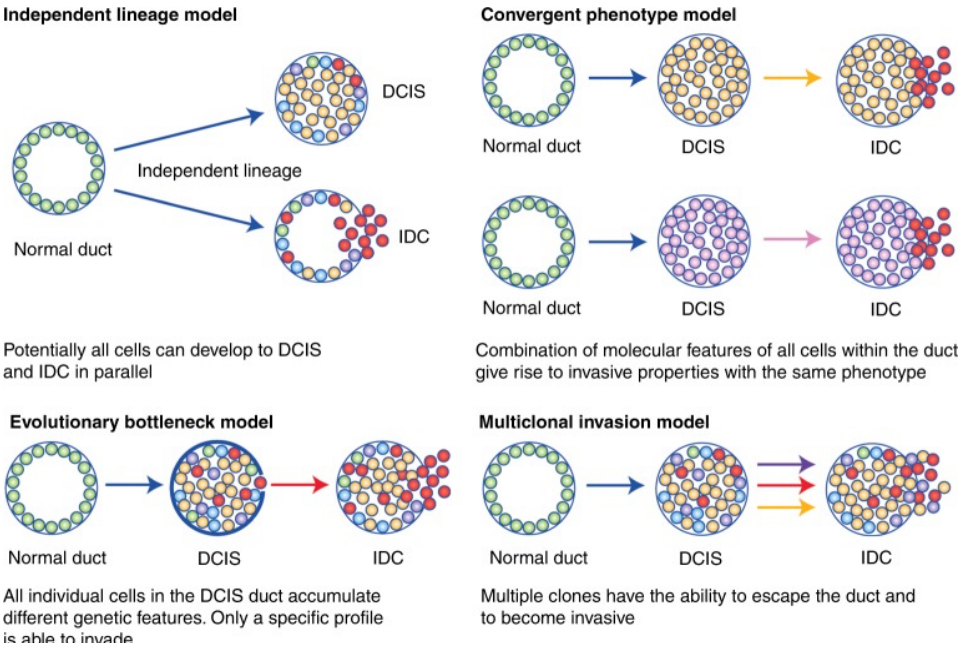

Figure 30: Overview of models showing four different theories of progression from ductal carcinoma in situ to invasive breast cancer.

Through current trials one tries to find out, in future if you can do without radiation or surgery in low-risk patients and to avoid the burden of overtreatment. Multigene-analysis should help to predict the risk of recurrence.

The current European studies called LORD and LORIS compare the security of active surveillance by having mammograms once a year for 10 years in opposite to the standard therapy (Fig. 31).

	COMET	LORIS	LORD
Inclusion criteria			
Age (years)	≥40	≥46	≥45
Nuclear grade	Low and intermediate	Low and intermediate (central pathology review on core biopsy or vacuum assisted biopsy)	Low
Morphology	Calcifications only	Calcifications only	Calcification only
Hormonal receptor	Oestrogen and progestrogen receptors positive and HER2 receptor negative (if applicable)	Not applicable	Not applicable
Exclusion criteria			
Symptoms	Exclude if symptomatic	Exclude if symptomatic	Exclude if symptomatic
Comedo-necrosis	Exclude	Exclude	Not applicable
Synchronous invasive cancer	Exclude	Exclude	Exclude
Bilaterality	Exclude bilateral	Include bilateral	Exclude bilateral
High risk	Include	Exclude if high risk (NICE guidelines)	Exclude for family history of BRCA carrier
History of chemoprevention	Exclude	Not applicable	Not applicable

Figure 31: Summary of the trial designs of the LORIS, LORD and COMET trials.

There is a strong hope in the research community that the trials LORD and LORIS represent a critical question that cannot be answered in any other way. Subtype stratification is essential. To find out the optimal treatment strategy it would be beneficial to determine the tumors invasive potential.
The aim is to identify in future which woman can avoid surgery and to find tailor treatment options for the affected patients.

It needs further research to come up with an accurate diagnosis and to determine the best possible therapy strategy for the patients to avoid over- and undertreatment.

There are some interesting approaches like Artificial intelligence image-based analysis. This is a method to identify breast lesions and predict the disease outcome and treatment response. It remains to be seen how this method can be implemented in everyday clinical practice.

Another aspect of research is concerned with circulating tumor cells (cTC) and circulating DNA (ctDNA). That are tumor cells, extending from the primary tumor cluster or metastasis, spread systemic in the blood- and lymph system (59). ctDNA- molecules are DNA-fragments of the tumor, finding in plasma or serum (59).
With this molecular investigation one tries to find reliable biomarkers for the efficiency of therapy. According to current research studies tumor cells can leave very early the primary tumor. This is how it was shown, that single tumor cells can already be detected in the bone marrow in 20% of the patients with DCIS (59).
In the future these biomarkers could be used as predictive biomarkers for a personalized therapy.

Further investigations and studies are necessary.

12. CONCLUSION

Further, the surgical excision is the gold standard in the management of DCIS with a safety distance of more than 2 mm. Mostly breast preserved therapy is possible with adjuvant radiation to minimize the risk of local recurrence. An extensive DCIS needed furthermore a mastectomy. Chemoprevention could be discussed specially in high-risk patients.

Classic LCIS diagnosed by core needle biopsy with radiologic-pathological concordant findings no routine surgical excision is necessary. Active surveillance and chemoprevention are management options. AGO and NCCN guidelines recommend surgical excision for variant LCIS and pleomorphic LCIS or classic LCIS with discordant imaging findings.

It is possible to deviate from the standard procedure, but this requires careful consideration of the individual circumstances and risk profile of the patient.
The management of patients with variant LCIS and low-risk DCIS will be further a challenge and a subject of debate.

13. ABBREVIATIONS

ADH	atypical ductal hyperplasia
AGO	Arbeitsgemeinschaft für gynäkologische Onkologie
AI	aromatase inhibitor
ALH	atypical lobular hyperplasia
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
CLCIS	classic lobular carcinoma in situ
CK	cytokeratin
ctDNA	circulating tumor DNA
cTC	circulating tumor cells
DNA	deoxyribonucleic acid
DCIS	ductal carcinoma in situ
ER	estrogen receptor
FDA	Food and Drug Administration
FLCIS	florid lobular carcinoma in situ
HER-2	human epidermal growth factor receptor
IBC	invasive breast cancer
IDC	invasive ductal carcinoma
ILC	invasive lobular carcinoma
LCIS	lobular carcinoma in situ
LIN	lobular intraepithelial neoplasia
LN	lobular neoplasia
MRI	magnetic resonance imaging
NCCN	National Comprehensive Centre Network
PLCIS	pleomorphic lobular carcinoma in situ
PR	progesterone receptor
SEER	Surveillance, Epidemiology, and End Results
SERM	selective estrogen receptor modulator
SLN	sentinel lymph node
TDLU	terminal duct lobular units
TNM	tumor, node, metastasis
UDH	usual ductal hyperplasia
USPSTF	U.S. preventive services Task Force
WHO	World Health Organisation

14. FIGURES

Figure 1: Histopathologic types of breast cancer, with relative incidences and prognoses. "Ductal carcinoma in situ" and „Lobular carcinoma in situ“.

Figure 2: Radiological findings DCIS
https://dx.doi.org/10.26044/ecr2019/C-1596

Figure 3: Mammographic mediolateral oblique view shows irregular mass (arrow) with pleomorphic calcifications in left area 1:30. (6)

Figure 4: Ultrasound image reveals subtle, hypoechoic, ovoid-shaped, 2cm mass (arrow) containing numerous echogenic foci. (6)

Figure 5: Early contrast-enhanced sagittal magnetic resonance image shows regional, non-mass enhancement (arrows) in the moderate background parenchymal enhancement. (6)

Figure 6: Low grade, cribriform. Medium power view of a terminal duct lobular unit involved by an intraductal epithelial proliferation with low grade nuclear atypia, cribriform growth pattern and microcalcifications. (11)

Figure 7: Intermediate grade, micropapillary. Intermediate power view of an intraductal epithelial proliferation with intermediate grade nuclear atypia, micropapillary growth pattern with focal necrosis. (11)

Figure 8: Intermediate grade, papillary. Intermediate power view of an intraductal epithelial proliferation with intermediate grade nuclear atypia, papillary growth pattern. (11)

Figure 9: Intermediate grade, solid. Intermediate power view of an intraductal epithelial proliferation with intermediate grade nuclear atypia, solid growth pattern with microcalcifications. (11)

Figure 10: High grade, flat. Medium power of an intraductal epithelial proliferation with high grade nuclear atypia, flat growth pattern and central necrosis. (11)

Figure 11: High-grade DCIS with central comedo-type necrosis.
https://www.researchgate.net/figure/High-grade-DCIS-with-central-comedo-type-necrosis_fig3_235897256

Figure 12: Nuclear grading of DCIS.
https://www.iheartpathology.net/post/breast-dcis

Figure 13: Classic LCIS, cell morphology. (6)

Figure 14: Type A cells. (6)

Figure 15: Type B cells. (6)

Figure 16: Pathologic features of pleomorphic lobular carcinoma in situ (PLCIS). A. Low power photomicrograph showing massive expansion of ducts and lobules by neoplastic cells, with associated comedo necrosis and calcifications (Original magnification 40x); B. High

power view of PLCIS with apocrine cytology showing dyshesive cells with nuclear pleomorphism and abundant eosinophilic cytoplasm (400x); C. High power view of PLCIS with non-apocrine cytology (400x). (32)

Figure 17: Florid lobular carcinoma in situ (LCIS). A. Florid LCIS has cytologic features identical to those of classic LCIS but is distinguished by marked distension of TDLUs or ducts, creating a confluent mass-like appearance at low power view. To qualify for florid subtype, an LCIS lesion should demonstrate at least one of the two architectural features depicted in B and C: (B) the spaces are expanded to a point that there is little to no intervening stroma between the markedly distended acini and ducts; (C) the expanded duct fills at least one high power field (an area equivalent to ~ 40 – 50 cells in diameter). Similar to pleomorphic LCIS, these lesions often demonstrate comedo necrosis. D. Florid LCIS with comedo necrosis and calcifications. Note the presence of classic LCIS with similar cytologic features at right lower corner, the presence of which should alert the pathologist the possibility of a LCIS subtype and not solid pattern DCIS. (32)

Figure 18: Histologic distinction between LCIS variants and DCIS. (39)

Figure 19: Expected expression of E-cadherin, p120 catenin. (39)

Figure 20: LCIS: Loss of E-cadherin expression. (39)

Figure 21: DCIS: E-cadherin positive. (39)

Figure 22: Intraductal proliferations.
https://www.iheartpathology.net/post/differences-between-udh-adh-dcis

Figure 23: Progression of ductal carcinoma in situ to invasive carcinoma from a histopathologic perspective. Representative micrographs and schematic representation of progressive stages of breast cancer including in situ carcinoma, microinvasive carcinoma and invasive carcinoma.
https://www.researchgate.net/figure/Progression-of-ductal-carcinoma-in-situ-to-invasive-carcinoma-from-a-histopathologic_fig1_334493450

Figure 24: Risk assessment, genetic counselling and genetic testing for BRCA-related cancer: clinical summary of the USPSTF recommendation.
https://www.aafp.org/pubs/afp/issues/2020/0215/p233.html

Figure 25: Follow-Up for invasive/non-invasive breast cancer (AGO Guidelines Version 2022).

Figure 26: Chemoprevention recommendation for low-dose Tamoxifen therapy in premalignant DCIS/ LCIS (AGO Guidelines Version 2022).

Figure 27: 10-year results of a phase 3 trial of low-dose tamoxifen in non-invasive breast cancer.

Figure 28: Prognostic Factors for local recurrence after DCIS (AGO Guidelines Version 2022)

Figure 29: Van Nuys Prognostic Index and recommendations for treatment. (65)

Figure 30: Overview of models showing four different theories of progression from ductal carcinoma in situ to invasive breast cancer. (2)

Figure 31: Summary of the trial designs of the LORIS, LORD and COMET trials. (2)

15. REFERENCES

1. Tomlinson-Hansen S, Khan M, Cassaro S. Breast Ductal Carcinoma in Situ. 2022 Sep 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 33620843.

2. van Seijen M, Lips EH, Thompson AM, Nik-Zainal S, Futreal A, Hwang ES, Verschuur E, Lane J, Jonkers J, Rea DW, Wesseling J; PRECISION team. Ductal carcinoma in situ: to treat or not to treat, that is the question. Br J Cancer. 2019 Aug;121(4):285-292. doi: 10.1038/s41416-019-0478-6. Epub 2019 Jul 9. PMID: 31285590; PMCID: PMC6697179.

3. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, Sapino A, Sasano H, Schnitt S, Sotiriou C, van Diest P, White VA, Lokuhetty D, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 World Health Organization classification of tumours of the breast. Histopathology. 2020 Aug;77(2):181-185. doi: 10.1111/his.14091. Epub 2020 Jul 29. PMID: 32056259.

4. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Breast cancer statistics, 2019. CA Cancer J Clin. 2019 Nov;69(6):438-451. doi: 10.3322/caac.21583. Epub 2019 Oct 2. PMID: 31577379.

5. Wen HY, Brogi E. Lobular Carcinoma In Situ. Surg Pathol Clin. 2018 Mar;11(1):123-145. doi: 10.1016/j.path.2017.09.009. Epub 2017 Dec 8. PMID: 29413653; PMCID: PMC5841603.

6. Vickery J, Biernacka A. Lobular carcinoma in situ (LCIS) classic. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/breastmalignantlcis.html. Accessed January 20th, 2023.

7. Jorns J, Sabel MS, Pang JC. Lobular neoplasia: morphology and management. Arch Pathol Lab Med. 2014 Oct;138(10):1344-9. doi: 10.5858/arpa.2014-0278-CC. PMID: 25268198.

8. Giannakeas V, Sopik V, Narod SA. Association of a Diagnosis of Ductal Carcinoma In Situ With Death From Breast Cancer. *JAMA Netw Open.* 2020;3(9):e2017124. doi:10.1001/jamanetworkopen.2020.17124

9. Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ. *JAMA Oncol.* 2015;1(7):888–896. doi:10.1001/jamaoncol.2015.2510

10. Tozbikian G. DCIS. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/breastmalignantdcis.html. Accessed January 20th, 2023.

11. Kerlikowske K. Epidemiology of ductal carcinoma in situ. J Natl Cancer Inst Monogr. 2010;2010(41):139-41. doi: 10.1093/jncimonographs/lgq027. PMID: 20956818; PMCID: PMC5161058.

12. Li, C.I.; Anderson, B.O., Daling, J.R. *et al.* Changing incidence of Lobular Carcinoma *in situ* of the Breast. *Breast Cancer Res Treat* **75,** 259-268 (2002). https://doi.org/10.1023/A:1019950918046

13. Li CI, Daling JR, Malone KE. Age-specific incidence rates of in situ breast carcinomas by histologic type, 1980 to 2001. Cancer Epidemiol Biomarkers Prev. 2005 Apr;14(4):1008-11. doi: 10.1158/1055-9965.EPI-04-0849. PMID: 15824180.

14. Friedewald SM, Rafferty EA, Rose SL, Durand MA, Plecha DM, Greenberg JS, Hayes MK, Copit DS, Carlson KL, Cink TM, Barke LD, Greer LN, Miller DP, Conant EF. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014 Jun 25;311(24):2499-507. doi: 10.1001/jama.2014.6095. PMID: 25058084.

15. Li JK, Wang HF, He Y, Huang Y, Liu G, Wang ZL. Ultrasonographic features of ductal carcinoma in situ: analysis of 219 lesions. Gland Surg. 2020 Dec;9(6):1945-1954. doi: 10.21037/gs-20-428. PMID: 33447545; PMCID: PMC7804561.

16. Tajima CC, de Sousa LLC, Venys GL, Guatelli CS, Bitencourt AGV, Marques EF. Magnetic resonance imaging of the breast: role in the evaluation of ductal carcinoma in situ. Radiol Bras. 2019 Jan-Feb;52(1):43-47. doi: 10.1590/0100-3984.2018.0058. PMID: 30804615; PMCID: PMC6383537.

17. Sokolova A, Lakhani SR. Lobular carcinoma in situ: diagnostic criteria and molecular correlates. Mod Pathol. 2021 Jan;34(Suppl 1):8-14. doi: 10.1038/s41379-020-00689-3. Epub 2020 Oct 6. PMID: 33024303.

18. Maxwell AJ, Clements K, Dodwell DJ, Evans AJ, Francis A, Hussain M, Morris J, Pinder SE, Sawyer EJ, Thomas J, Thompson A; Sloane Project Steering Group. The radiological features, diagnosis and management of screen-detected lobular neoplasia of the breast: Findings from the Sloane Project. Breast. 2016 Jun;27:109-15. doi: 10.1016/j.breast.2016.03.004. Epub 2016 Apr 6. PMID: 27060553.

19. Scoggins M, Krishnamurthy S, Santiago L, Yang W. Lobular carcinoma in situ of the breast: clinical, radiological, and pathological correlation. Acad Radiol. 2013 Apr;20(4):463-70. doi: 10.1016/j.acra.2012.08.020. Erratum in: Acad Radiol. 2013 Jun;20(6):790. PMID: 23498988.

20. Consensus Conference on the classification of ductal carcinoma in situ. The Consensus Conference Committee. Cancer. 1997 Nov 1;80(9):1798-802. doi: 10.1002/(sici)1097-0142(19971101)80:9<1798::aid-cncr15>3.0.co;2-0. PMID: 9351550.

21. Lester SC, Bose S, Chen YY, Connolly JL, de Baca ME, Fitzgibbons PL, Hayes DF, Kleer C, O'Malley FP, Page DL, Smith BL, Weaver DL, Winer E; Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast. Arch Pathol Lab Med. 2009 Jan;133(1):15-25. doi: 10.5858/133.1.15. PMID: 19123730.

22. Sneige N, Wang J, Baker BA, Krishnamurthy S, Middleton LP. Clinical, histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in situ of the breast: a report of 24 cases. Mod Pathol. 2002 Oct;15(10):1044-50. doi: 10.1097/01.MP.0000027624.08159.19. PMID: 12379750.

23. Chen YY, Hwang ES, Roy R, DeVries S, Anderson J, Wa C, Fitzgibbons PL, Jacobs TW, MacGrogan G, Peterse H, Vincent-Salomon A, Tokuyasu T, Schnitt SJ, Waldman FM. Genetic and phenotypic characteristics of pleomorphic lobular carcinoma in situ of the breast. Am J Surg Pathol. 2009 Nov;33(11):1683-94. doi: 10.1097/PAS.0b013e3181b18a89. PMID: 19701073; PMCID: PMC2783988.

24. Schnitt SJ, Brogi E, Chen YY, King TA, Lakhani SR. American Registry of Pathology Expert Opinions: The Spectrum of Lobular Carcinoma in Situ: Diagnostic Features and Clinical Implications. Ann Diagn Pathol. 2020 Apr;45:151481. doi: 10.1016/j.anndiagpath.2020.151481. Epub 2020 Feb 15. PMID: 32120324; PMCID: PMC7401835.

25. Mohsin SK, O'Connell P, Allred DC, Libby AL. Biomarker profile and genetic abnormalities in lobular carcinoma in situ. Breast Cancer Res Treat. 2005 Apr;90(3):249-56. doi: 10.1007/s10549-004-4493-8. PMID: 15830138.

26. Dabbs DJ, Schnitt SJ, Geyer FC, Weigelt B, Baehner FL, Decker T, Eusebi V, Fox SB, Ichihara S, Lakhani SR, Palacios J, Rakha E, Richardson AL, Schmitt FC, Tan PH, Tse GM, Vincent-Salomon A, Ellis IO, Badve S, Reis-Filho JS. Lobular neoplasia of the breast revisited with emphasis on the role of E-cadherin immunohistochemistry. Am J Surg Pathol. 2013 Jul;37(7):e1-11. doi: 10.1097/PAS.0b013e3182918a2b. PMID: 23759937.

27. Go EM, Chan SK, Vong JS, Lui PC, Chan AW, Ma TK, Ang MA, Law BK, Tan PH, Tse GM. Predictors of invasion in needle core biopsies of the breast with ductal carcinoma in situ. Mod Pathol. 2010 May;23(5):737-42. doi: 10.1038/modpathol.2009.187. Epub 2010 Jan 15. PMID: 20081814.

28. Barbalaco Neto G, Rossetti C, Fonseca FL, Valenti VE, de Abreu LC. Ductal carcinoma in situ in core needle biopsies and its association with extensive in situ component in the surgical specimen. Int Arch Med. 2012 Jun 20;5:19. doi: 10.1186/1755-7682-5-19. PMID: 22715888; PMCID: PMC3432016.

29. https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/breast-biopsy.html

30. https://www.captodayonline.com/lcis-variants-dcis-tips-telling-apart/2/

31. Tingfeng Shen, Jiajia He, Deyong Kang, Gangqin Xi, Zhong Chen, Wenjiao Ren, Jianxin Chen, "Identifying classic and florid lobular carcinoma in situ using multiphoton microscopy," Proc. SPIE 11209, Eleventh International Conference on Information Optics and Photonics (CIOP 2019), 112092T (20 December 2019); https://doi.org/10.1117/12.2548596

32. Shaaban, A.M. Why is LCIS Important–Pathological Review. *Curr Breast Cancer Rep* **13**, 132–140 (2021). https://doi.org/10.1007/s12609-021-00415-1

33. https://surgpathcriteria.stanford.edu/breast/flat_epithelial_atypia/

34. Tomlinson-Hansen S, Khan M, Cassaro S. Atypical Ductal Hyperplasia. 2022 Apr 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 32965915.

35. https://www.cancer.org/cancer/breast-cancer/non-cancerous-breast-conditions/hyperplasia-of-the-breast-ductal-or-lobular.html

36. Kim M, Kim HJ, Chung YR, Kang E, Kim EK, Kim SH, Kim YJ, Kim JH, Kim IA, Park SY. Microinvasive Carcinoma versus Ductal Carcinoma *In Situ*: A Comparison of Clinicopathological Features and Clinical Outcomes. J Breast Cancer. 2018 Jun;21(2):197-205. doi: 10.4048/jbc.2018.21.2.197. Epub 2018 Jun 20. PMID: 29963116; PMCID: PMC6015981.

37. Myers DJ, Walls AL. Atypical Breast Hyperplasia. 2022 Feb 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 29261937.

38. Muller KE, Roberts E, Zhao L, Jorns JM. Isolated Atypical Lobular Hyperplasia Diagnosed on Breast Biopsy: Low Upgrade Rate on Subsequent Excision With Long-Term Follow-up. Arch Pathol Lab Med. 2018 Mar;142(3):391-395. doi: 10.5858/arpa.2017-0155-OA. Epub 2017 Nov 21. PMID: 29160721.

39. https://acsjounals.onlinelibrary.wiley.com/doi/full/10.3322/caas.21393

40. https://www.cancer.org/cancer/breast-cancer/risk-and-prevention/breast-cancer-risk-factors-you-cannot-change.html

41. https://wispecialists.com/what-the-tyrer-cuzick-score-means-for-breast-health/

42. https://www.nccn.org/guidelines/category_1

43. https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma

44. Lee LA, Silverstein MJ, Chung CT, Macdonald H, Sanghavi P, Epstein M, Holmes DR, Silberman H, Ye W, Lagios MD. Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-in-situ of the breast. Am J Surg. 2006 Oct;192(4):416-9. doi: 10.1016/j.amjsurg.2006.06.005. PMID: 16978940.

45. Allred DC, Anderson SJ, Paik S, Wickerham DL, Nagtegaal ID, Swain SM, Mamounas EP, Julian TB, Geyer CE Jr, Costantino JP, Land SR, Wolmark N. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol. 2012 Apr 20;30(12):1268-73. doi: 10.1200/JCO.2010.34.0141. Epub 2012 Mar 5. PMID: 22393101; PMCID: PMC3341142.

46. Nakhlis F, Baker GM, Pilewskie M, Gelman R, Calvillo KZ, Ludwig K, McAuliffe PF, Willey S, Rosenberger LH, Parker C, Gallagher K, Jacobs L, Feldman S, Lange P, DeSantis SD, Schnitt SJ, King TA. The Incidence of Adjacent Synchronous Invasive Carcinoma and/or Ductal Carcinoma In Situ in Patients with Intraductal Papilloma without Atypia on Core Biopsy: Results from a Prospective Multi-Institutional Registry (TBCRC 034). Ann Surg Oncol. 2021 May;28(5):2573-2578. doi: 10.1245/s10434-020-09215-w. Epub 2020 Oct 12. PMID: 33047246.

47. https://www.breastsurgeons.org/new_layout/about/statements/index.php#consensus_statements

48. Trivedi MS, Coe AM, Vanegas A, Kukafka R, Crew KD. Chemoprevention Uptake among Women with Atypical Hyperplasia and Lobular and Ductal Carcinoma *In Situ*. Cancer Prev Res (Phila). 2017 Aug;10(8):434-441. doi: 10.1158/1940-6207.CAPR-17-0100. Epub 2017 Jun 13. PMID: 28611039; PMCID: PMC5540777.

49. Crew KD, Silverman TB, Vanegas A, Trivedi MS, Dimond J, Mata J, Sin M, Jones T, Terry MB, Tsai WY, Kukafka R. Study protocol: Randomized controlled trial of web-based decision support tools for high-risk women and healthcare providers to increase breast cancer chemoprevention. Contemp Clin Trials Commun. 2019 Aug 22;16:100433. doi: 10.1016/j.conctc.2019.100433. Erratum in: Contemp Clin Trials Commun. 2020 Dec 10;20:100689. PMID: 31497674; PMCID: PMC6722284.

50. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, McTiernan A, Robbins J, Johnson KC, Martin LW, Winquist E, Sarto GE, Garber JE, Fabian CJ, Pujol P, Maunsell E, Farmer P, Gelmon KA, Tu D, Richardson H; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011 Jun 23;364(25):2381-91. doi: 10.1056/NEJMoa1103507. Epub 2011 Jun 4. Erratum in: N Engl J Med. 2011 Oct 6;365(14):1361. PMID: 21639806.

51. Cuzick J, Sestak I, Forbes JF, Dowsett M, Cawthorn S, Mansel RE, Loibl S, Bonanni B, Evans DG, Howell A; IBIS-II investigators. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2020 Jan 11;395(10218):117-122. doi: 10.1016/S0140-6736(19)32955-1. Epub 2019 Dec 12. Erratum in: Lancet. 2020 Feb 15;395(10223):496. Erratum in: Lancet. 2021 Feb 27;397(10276):796. PMID: 31839281; PMCID: PMC6961114.

52. Visvanathan K, Chlebowski RT, Hurley P, Col NF, Ropka M, Collyar D, Morrow M, Runowicz C, Pritchard KI, Hagerty K, Arun B, Garber J, Vogel VG, Wade JL, Brown P, Cuzick J, Kramer BS, Lippman SM; American Society of Clinical Oncology. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J Clin Oncol. 2009 Jul 1;27(19):3235-58. doi: 10.1200/JCO.2008.20.5179. Epub 2009 May 26. PMID: 19470930; PMCID: PMC2716943.

53. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, Caviglia S, Avino F, Cortesi L, Taverniti C, Pacquola MG, Falcini F, Gulisano M, Digennaro M, Cariello A, Cagossi K, Pinotti G, Lazzeroni M, Serrano D, Branchi D, Campora S, Petrera M, Buttiron Webber T, Boni L, Bonanni B. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. J Clin Oncol. 2019 Jul 1;37(19):1629-1637. doi: 10.1200/JCO.18.01779. Epub 2019 Apr 11. PMID: 30973790; PMCID: PMC6601429.

54. Rakovitch E, Nofech-Mozes S, Hanna W, Baehner FL, Saskin R, Butler SM, Tuck A, Sengupta S, Elavathil L, Jani PA, Bonin M, Chang MC, Robertson SJ, Slodkowska E, Fong C, Anderson JM, Jamshidian F, Miller DP, Cherbavaz DB, Shak S, Paszat L. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat. 2015 Jul;152(2):389-98. doi: 10.1007/s10549-015-3464-6. Epub 2015 Jun 29. PMID: 26119102; PMCID: PMC4491104.

55. https://ecancer.org/en/news/6756-sabcs-2014-multigene-test-can-predict-risk-of-disease-recurrence-for-women-with-ductal-carcinoma-in-situ

56. Silverstein MJ, Lagios MD, Craig PH, Waisman JR, Lewinsky BS, Colburn WJ, Poller DN. A prognostic index for ductal carcinoma in situ of the breast. Cancer. 1996 Jun 1;77(11):2267-74. doi: 10.1002/(SICI)1097-0142(19960601)77:11<2267::AID-CNCR13>3.0.CO;2-V. PMID: 8635094.

57. Kunkiel, M., Niwińska, A. Assessment of the usefulness of prognostic Van Nuys Prognostic Index in the treatment in ductal carcinoma in situ in 15-year observation. *Sci Rep* **11**, 22645 (2021). https://doi.org/10.1038/s41598-021-02126-0

58. McDivitt RW, Hutter RV, Foote FW Jr, Stewart FW. In situ lobular carcinoma. A prospective follow-up study indicating cumulative patient risks. JAMA. 1967 Jul 10;201(2):82-6. doi: 10.1001/jama.201.2.82. PMID: 6072345.

59. Sänger N, Effenberger KE, Riethdorf S, Van Haasteren V, Gauwerky J, Wiegratz I, Strebhardt K, Kaufmann M, Pantel K. Disseminated tumor cells in the bone marrow of patients with ductal carcinoma in situ. Int J Cancer. 2011 Nov 15;129(10):2522-6. doi: 10.1002/ijc.25895. Epub 2011 Mar 25. PMID: 21207426.