REVIEW ARTICLE

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An update on intraductal and intralobular proliferative lesions of the breast

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INTRODUCTION

Intraductal and intralobular proliferative lesions or epithelial hyperplasias of the breast comprise a heterogeneous spectrum of proliferations that generally originate in the terminal duct-lobular units (TDLUs) of the breast and are confined to the ductal-lobular system[1]. Such lesions are subdivided into two major categories based on cytological and architectural criteria: ductal and lobular. The magnitude of the risk of subsequent breast cancer varies widely, and part of these proliferations represent risk indicators, whereas others act as true precursors of invasive breast carcinomas (IBCs)[1-5].

Since 2012, the classification of breast tumors according to the World Health Organization (WHO) has adopted the traditional nomenclature of "intraductal and intralobular proliferative lesions" (Tables 1 and 2), and previous terminologies like "breast intraductal neoplasia" and "lobular intraepithelial neoplasia" proposed by Tavassoli have been withdrawn[1].

INTRADUCTAL PROLIFERATIVE LESIONS

Intraductal proliferative lesions are grouped into three classes based on cytological and architectural criteria: usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS)[1]. Moreover, there is the

Table 2. Histopathological classification of precursor lesions of the breast.

Precursor lesions
Atypical ductal hyperplasia
Flat epithelial atypia
Ductal carcinoma in situ
Noninvasive lobular neoplasia
Atypical lobular hyperplasia
Lobular carcinoma in situ
Classic lobular carcinoma in situ
Pleomorphic lobular carcinoma in situ
Florid lobular carcinoma in situ

WHO classification of breast tumors (5th edition, 2019).

Dupont and Page (1985)	Tavassoli (1998)	WHO (2012 and 2019)
Mild ductal hyperplasia	Usual ductal hyperplasia	Usual ductal hyperplasia
Moderate ductal hyperplasia without atypia		
	Ductal intraepithelial neoplasia grade 1A (DIN 1A)	Columnar cell lesion - Columnar cell change - Columnar cell hyperplasia - Flat epithelial atypia
Atypical ductal hyperplasia	Ductal intraepithelial neoplasia grade 1B (DIN 1B)	Atypical ductal hyperplasia
Low-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade 1C (DIN 1C)	Low-grade ductal carcinoma in situ
Intermediate-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade 2 (DIN 2)	Intermediate-grade ductal carcinoma in situ
High-grade ductal carcinoma in situ	Ductal intraepithelial neoplasia grade (DIN 3)	High-grade ductal carcinoma in situ

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group of columnar cell lesions (CCLs)[1], which will be discussed separately.

Usual ductal hyperplasia

In general, UDH represents an incidental finding in breast biopsies that is morphologically composed of a polymorphic population of benign epithelial cells displayed in a haphazard orientation, regularly forming secondary lumina and fenestrations, in a slit-like fashion (Figure 1). The proliferations may show a solid, streaming, or micropapillary pattern. UDH cells have indistinct borders and are irregularly organized, with variably sized nuclei, frequently exhibiting intranuclear cytoplasmic inclusions and grooves. Immunohistochemistry demonstrates a mixed phenotype of UDH cells, with heterogeneous positivity for high-molecular-weight cytokeratins (CK 5/6, CK14, and 34βE12) and estrogen receptor (ER)[1].

Long-term follow-up studies have determined that women diagnosed with UDH have a slight increase in the risk for subsequent breast cancer (1.5- to 2-fold relative risk [RR])[3-5].

Atypical ductal hyperplasia

Atypical ductal hyperplasia is a clonal, epithelial proliferative lesion with cytological architectural characteristics analogous to those of low-grade DCIS, although with partial involvement of ductal spaces and/or a limited extent[1,6]. Clinically, lesions are often detected by screening mammography due to the association with microcalcifications, accounting for 2–14% of diagnoses in breast biopsies in the context of screened populations[6].

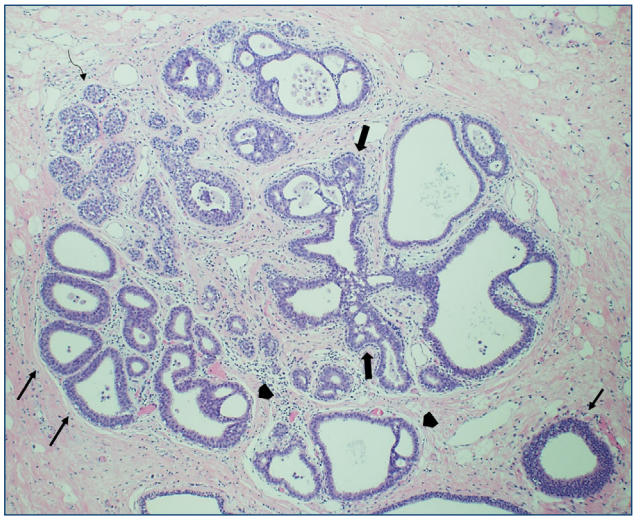

Figure 1. A histological section stained with H&E showing multiple epithelial proliferative lesions of the breast: usual ductal hyperplasia (thick arrows); atypical ductal hyperplasia (arrowheads); flat epithelial atypia (thin arrows); and classic noninvasive lobular neoplasia (curved arrow).

For the distinction from low-grade DCIS, Page et al. proposed a cutoff value of ≤2 mm in the contiguous dimension or less than two completely involved spaces. ADH cells are monomorphic, with round nuclei and dense chromatin. They are evenly spaced and are disposed in rigid bridges, arcades, and bars, forming bulbous micropapillae or well-developed secondary spaces in a cribriform pattern (Figure 1). Unlike UDH, ADH cells typically demonstrate diffuse and strong expression of ER and lack staining for CK5/6, with an immunophenotype that parallels other lesions in the low-grade breast neoplasia pathway (CCL, low-grade DCIS, and classic noninvasive lobular neoplasia [n-LN]). The main differential diagnoses of ADH include low-grade DCIS, collagenous spherulosis, and micropapillary UDH (gynecomastoid hyperplasia)[1,3,6].

The RR associated with ADH for the development of IBC is 3- to 5-fold, while the absolute risk is 1% per year in 25 years[3-5]. Antiestrogen chemoprevention significantly decreases the risk of future breast cancer. For ADH detected on core needle biopsy (CNB), according to contemporary series with imaging-pathological correlation, the upgrade rate to DCIS or IBC ranges from 10 to 20%. Therefore, current guidelines recommend surgical excision for patients with this CNB diagnosis[6-9].

Ductal carcinoma in situ

Clinical presentation and epidemiology

Before the advent of imaging screening programs, DCIS represented only 2–3% of palpable breast cancers. Afterward, the incidence has increased, and nowadays it comprises 20–25% of newly diagnosed breast cancers in the United States[1,10,11]. The mean age at diagnosis varies from 50 to 59 years, and 80–85% of DCIS is detected by mammography that typically shows unilateral calcifications. On magnetic resonance imaging (MRI), a non-mass-like enhancement may be seen. Occasionally, DCIS may present as a palpable nodule, nipple discharge, or Paget disease[1,10,11].

Definition and morphological features

Ductal carcinoma in situ encompasses a morphologically, biologically, genetically, and clinically heterogeneous group of lesions defined as a noninvasive, epithelial neoplastic proliferation confined to the mammary ductal-lobular system and that represents a nonobligate precursor of IBC[1].

Histologically, DCIS is a unifocal disease categorized as being of low (grade I), intermediate (grade II), or high (grade III) nuclear grade, based on cytonuclear morphology. Low-grade lesions measure more than 2 mm and are constituted by small, monotonous cells with uniform nuclei, regular chromatin, and

inconspicuous nucleoli, which show polarization around the involved spaces. Nuclei size is 1.5–2 times that of a red blood cell, and mitotic figures are sparse. Necrosis is also rare. In contrast, high-grade DCIS is composed of large, atypical cells with big, pleomorphic nuclei (>2.5 times the size of a red blood cell), coarse chromatin, and prominent nucleoli. Mitoses are frequent, as well as comedonecrosis and calcifications. DCIS of intermediate nuclear grade displays cells with a moderate variation in size, shape, and polarization. Necrosis may be found, both punctate and comedo types[1].

Architectural patterns include comedo, solid, cribriform, micropapillary, and papillary. Paget disease is one of the presentations of high-grade DCIS, which extends to the epidermis of the nipple[1].

In addition to the nuclear grade, pathological reports have to mention architectural patterns, presence and type of necrosis, presence and site of microcalcifications, size of the lesion, status, and distance to surgical margins[1].

Differential diagnoses comprise UDH, ADH, lobular carcinoma in situ, invasive cribriform carcinoma, and adenoid cystic carcinoma.

Immunohistochemical and molecular findings

Estrogen receptor expression in DCIS is observed in 75% of cases, whereas HER2 (epidermal growth factor receptor family member 2) overexpression is found in 40%. Currently, ER is the only predictive marker recommended in guidelines for routine clinical use in DCIS in order to select patients for anti-estrogen therapy. PR testing is optional[1].

Non-high-grade DCIS is generally ER+/HER2- and has fewer copy number alterations than high-grade DCIS. Many aberrations are recurrent in the latter, including alterations in known cancer genes such as *MYC* (gain at 8q22–24), *CCND1* (gain at 11q13), and *ERBB2* (gain at 17q12). Most driver mutations observed in DCIS are also found in IBCs, with the most common mutated genes being *PIK3CA* and *TP53*[12-15].

Prognosis and follow-up

If untreated, patients diagnosed with DCIS have a 10-fold risk of developing ipsilateral IBC. However, the breast cancer-specific risk associated with DCIS is extremely favorable. Data on its natural history are limited, and about 50% of recurrences after breast-conserving surgery (BCS) occur as IBC. Several factors have been described in association with a higher relapse risk: younger age, large lesion size, high nuclear grade, comedonecrosis, and positive margins. In patients who underwent breast radiation therapy, outcome analyses have consistently demonstrated a 50% reduction in local ipsilateral recurrence. Similarly, adjuvant hormone therapy decreases the risk of relapse, even though this benefit is restricted to ER-positive disease. Currently, the standard of care for DCIS patients is either BCS with clear margins (ideally ≥2 mm) and radiotherapy with or without hormone therapy or mastectomy[1,9,13,15-17].

INTRALOBULAR PROLIFERATIVE LESIONS: NONINVASIVE LOBULAR NEOPLASIA

Non-invasive lobular neoplasia refers to the spectrum of atypical epithelial proliferative lesions characterized by cell dyshesion consequent to the functional alteration or loss of E-cadherin-mediated cell adhesion[1]. According to the definition by the World Health Organization (WHO) Classification of Tumors of the Breast, 5th ed., this designation comprises atypical lobular hyperplasia (ALH) and classic lobular carcinoma in situ (C-LCIS), as well as two LCIS variants, specifically florid LCIS (F-LCIS) and pleomorphic LCIS (P-LCIS)[1]. ALH and C-LCIS can be denoted together as classic lobular neoplasia (c-LN) (Figure 1).

Clinical presentation and epidemiology

The estimation of the real incidence of n-LN is challenging, but it is projected to vary from 0.5 to 4% of benign breast biopsies[1,2,18].

Clinically, c-LN predominantly affects premenopausal women, and the median age at diagnosis is 50–55 years, while LCIS variants tend to occur in older patients with a median age of 59–61 years[1,19]. C-LCIS is described as multicentric in up to 85% of cases and bilateral in 30–67%. Of interest, c-LN is asymptomatic and usually represents an incidental finding in breast specimens obtained to assess other lesions. Although mammographically silent, it can be identified by an MRI examination[20]. Conversely, F-LCIS and P-LCIS tend to have unifocal and continuous distribution and are regularly detected mammographically due to the presence of pleomorphic calcifications, architectural distortion, and mass lesions with or without associated calcifications. In addition, both variants of LCIS are generally diagnosed in association with invasive lobular carcinoma (ILC)[21,22].

Definition and morphological features

Classic LCIS, as defined by Foote and Stewart, is characterized by the proliferation of noncohesive, nonpolarized, uniform, and round cells with low nuclear grade, which fill and distend more than 50% of the acini of the TDLUs[1,23]. Intracytoplasmic mucin vacuoles are often found, while mitotic figures are rare.

Two population cell types can be encountered, alone or in combination: type A and type B cells. Type A cells are small and exhibit a scant cytoplasm, with monotonous nuclei and dense chromatin; type B cells are rather larger, have more cytoplasm, and display slightly bigger nuclei with inconspicuous nucleoli[1].

The differential diagnosis includes ALH, low-grade DCIS with a predominantly solid architectural pattern, myoepithelial hyperplasia, and clear cell change of the epithelium of the TDLUs[1].

ALH consists of cells morphologically identical to those of C-LCIS. However, the extent is limited, and the lesion involves less than 50% of the acini of the TDLUs, with minimal expansion[1].

Both lesions commonly coexist and may demonstrate ductal pagetoid involvement[1].

Florid LCIS was first described by Fadare et al., and it was initially referred to as "LCIS with comedonecrosis"[24]. This lesion is composed of type A and/or type B cells analogous to those of classic LCIS, but they fill multiple TDLUs with massive acinar distension and little to no intervening stroma, frequently forming nodular aggregates, with an architecture that differs from C-LCIS. Central comedonecrosis and calcifications may be found, although their presence is not required for the diagnosis. The main distinction is with solid DCIS with low-to-intermediate nuclear grade[1,21,24].

Pleomorphic LCIS is constituted by big discohesive cells with marked nuclear atypia, large nuclei (four times larger than the size of a lymphocyte), coarse chromatin, and prominent nucleoli. Neoplastic cells usually have more cytoplasm and mitoses. Central necrosis with calcifications is frequently seen. The key differential diagnosis is with high-grade DCIS[1]. This variant was first recognized by Sneige et al.,[25] and since then, the number of reported cases of P-LCIS not associated with invasive carcinoma remains limited. Moreover, a subset of P-LCIS is composed of ovoid to plasmacytoid cells with large nucleoli and abundant eosinophilic, granular cytoplasm which is called apocrine P-LCIS[1,21,22,25].

Immunohistochemical and molecular findings

The dysfunction of E-cadherin represents the hallmark feature that defines all lobular lesions. It is a transmembrane glycoprotein encoded by the *CDH1* gene (16q22.1), which plays a critical role in cell-to-cell adhesion and forms a complex with β-catenin, α-catenin, and p120-catenin. Therefore, n-LN is characteristically distinguished by the loss of membranous expression of E-cadherin and β-catenin is on immunohistochemistry, as well as the cytoplasmic distribution of p120 catenin[1,25,26]. However, 15% of all subtypes of lobular neoplasia show cytoplasmic staining or retain some membrane reactivity for E-cadherin ("aberrant" expression), though with a reduced intensity/fragmented pattern. In contrast, benign ductal cells and DCIS cells show strong, uniform membrane positivity for E-cadherin, β-catenin, and p120 catenin[1].

Typically, ALH, C-LCIS, and F-LCIS demonstrate strong and diffuse positivity for ER and PR and lack HER2 overexpression[1,20,23]. Even though P-LCIS is regularly ER-positive/HER2-negative, approximately 13–30% of cases exhibit negativity for ER and HER2 overexpression, particularly in apocrine P-LCIS[1,22,25].

Molecular studies have demonstrated that LCIS is a clonal proliferation that harbors recurrent chromosomal loss at 16q and gain at 1q. Furthermore, F-LCIS and P-LCIS present greater genomic instability than C-LCIS, showing increased copy-number aberrations and gene amplifications. The most commonly mutated genes include *CDH1* (81% of cases), *PIK3CA* (41%), and *CBFB* (12%). Interestingly, previous reports have uncovered that LCIS and ILC can be clonally related and share molecular alterations. These observations support that n-LN is not only a high-risk lesion but also a nonobligate precursor of ILC[1,26-28].

Prognosis and follow-up

Lobular carcinoma in situ represents a risk factor as well as a nonobligate precursor, IBC, either lobular or no special type/ductal. For patients diagnosed with C-LCIS, the RR for the development of subsequent breast cancer varies from 8 to 10 times the risk expected in women without this lesion, and the absolute risk is 1–2% per year, leading to a cumulative rate of more than 20% at 20 years. For women with C-LCIS, the 20-year breast cancer-specific survival rate is superior to 90%[1,2,19,29]. Among patients with ALH, the RR is 4–6 times the risk in the general population, whereas the absolute risk is about 1% per year[1,30].

Given this background, active surveillance of patients with c-LN and no suspicious clinical/imaging findings is currently favored over surgical management, and antiestrogen chemoprevention lowers the risk of subsequent breast cancer[31]. The surgical management of c-LN detected at CNB has remained arguable. If LCIS is not the radiological target lesion and once cases with radiological-pathological discordance are excluded, excisional upgrade rates of incidental c-LN decrease to 1–4%[1,8,32,33]. Hence, guidelines by the American Society of Breast Surgeons recommend follow-up over surgery for women diagnosed with only c-LN in CNB and imaging-histological concordant findings. Of note, reporting of margin status for ALH and C-LCIS is not required[9].

Regarding LCIS variants, the natural history remains poorly understood, and optimal treatment is unclear. As many as 87% of cases are associated with invasive carcinomas at diagnosis. Moreover, around 25–60% of cases of F-LCIS and P-LCIS documented on CNB are upgraded to carcinoma upon excision[1,8,32,33]. Consequently, surgical resection is mandatory after the detection of these LCIS variants in CNB. Recurrence rates of P-LCIS treated with BCS range from 0 to 57%. The potential benefit of adjuvant radiation therapy and the prognostic impact of a positive margin status are not well established, although data from follow-up studies support that surgical excision should try to achieve clear margins, and pathologists thus need to report margin status for both P-LCIS and F-LCIS[1,21,22].

Finally, both classic and nonclassic LCIS are no longer staged as pTis according to the eighth edition of the American Joint Committee on Cancer TNM classification[1].

COLUMNAR CELL LESIONS

Columnar cell lesions of the breast include columnar cell change (CCC), columnar cell hyperplasia (CCH), and flat epithelial atypia (FEA). They represent clonal alterations of the TDLU and are marked by the presence of unevenly enlarged and dilated acini lined by columnar epithelial cells. These lesions are frequently detected on mammography as a result of the association with calcifications[1].

Lesions in which the epithelial cell lining of TDLUs is only 1–2 cell layers thick are classified as CCC, while CCH is designated for those with>2 cell layers. Cellular stratification and tufting are common, and cytological atypia is absent. FEA is characterized by low-grade cytological atypia, and the acini of involved TDLUs are lined by one to several layers of monotonous cuboidal to columnar cells (Figure 1), regularly with prominent apical snouts[1]. Complex architectural proliferations are not encountered. Furthermore, FEA is frequently associated with ADH, low-grade DCIS, n-LN, and low-grade IBCs, sharing molecular alterations with these lesions[34].

The risk of progression to IBC seems to be very low, and surgical excision upon a CNB diagnosis of FAE is controversial. Radiological-pathological correlation is mandatory for guiding further management, and patients may be spared resection if a postbiopsy mammogram documents that all calcifications have been removed[1,8,35,36].

CONCLUSION

Knowledge of diagnostic criteria is essential for the accurate recognition and classification of epithelial proliferative lesions of the breast, which will define management and help estimate the risk for the development of subsequent IBC.

AUTHORS' CONTRIBUTIONS

RFA: Writing – original draft. **HG:** Writing – review & editing. **MDB:** Conceptualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. International Agency for Research on Cancer. WHO classification of tumours editorial board. Breast tumours. WHO classification of tumour series. 5th ed. Lyon: International Agency for Research on Cancer; 2019.
2. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast--risk assessment and management options. N Engl J Med. 2015;372(1):78-89. https://doi.org/10.1056/NEJMsr1407164
3. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med. 1985;312(3):146-51. https://doi.org/10.1056/NEJM198501173120303
4. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353(3):229-37. https://doi.org/10.1056/NEJMoa044383
5. Collins LC, Baer HJ, Tamimi RM, Connolly JL, Colditz GA, Schnitt SJ. The influence of family history on breast cancer risk in women with biopsy-confirmed benign breast disease: results from the nurses' health study. Cancer. 2006;107(6):1240-7. https://doi.org/10.1002/cncr.22136
6. Sanders ME, Podoll MB. Atypical ductal hyperplasia-ductal carcinoma in situ spectrum: diagnostic considerations and treatment impact in the era of deescalation. Surg Pathol Clin. 2022;15(1):95-103. https://doi.org/10.1016/j.path.2021.11.006
7. Collins LC, Aroner SA, Connolly JL, Colditz GA, Schnitt SJ, Tamimi RM. Breast cancer risk by extent and type of atypical hyperplasia: an update from the nurses' health studies. Cancer. 2016;122(4):515-20. https://doi.org/10.1002/cncr.29775
8. Harbhajanka A, Gilmore HL, Calhoun BC. High-risk and selected benign breast lesions diagnosed on core needle biopsy: evidence for and against immediate surgical excision. Mod Pathol. 2022;35(11):1500-8. https://doi.org/10.1038/s41379-022-01092-w
9. American Society Breast Surgeons. Consensus guideline on concordance assessment of image-guided breast biopsies and management of borderline or high-risk lesions. 2023 [cited on 2023 Mar 2]. Available from: https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Concordance-Assessment-of-Image-Guided-Breast-Biopsies.pdf
10. Stomper PC, Margolin FR. Ductal carcinoma in situ: the mammographer's perspective. AJR Am J Roentgenol. 1994;162(3):585-91. https://doi.org/10.2214/ajr.162.3.8109501

11. Weaver DL, Rosenberg RD, Barlow WE, Ichikawa L, Carney PA, Kerlikowske K, et al. Pathologic findings from the breast cancer surveillance consortium: population-based outcomes in women undergoing biopsy after screening mammography. Cancer. 2006;106(4):732-42. https://doi.org/10.1002/cncr.21652
12. Bergholtz H, Kumar S, Wärnberg F, Lüders T, Kristensen V, Sørlie T. Comparable cancer-relevant mutation profiles in synchronous ductal carcinoma in situ and invasive breast cancer. Cancer Rep (Hoboken). 2020;3(3):e1248. https://doi.org/10.1002/cnr2.1248
13. Pareja F, Brown DN, Lee JY, Da Cruz Paula A, Selenica P, Bi R, et al. Whole-exome sequencing analysis of the progression from non-low-grade ductal carcinoma in situ to invasive ductal carcinoma. Clin Cancer Res. 2020;26(14):3682-93. https://doi.org/10.1158/1078-0432.CCR-19-2563
14. Agahozo MC, Sieuwerts AM, Doebar SC, Verhoef EI, Beaufort CM, Ruigrok-Ritstier K, et al. PIK3CA mutations in ductal carcinoma in situ and adjacent invasive breast cancer. Endocr Relat Cancer. 2019;26(5):471-82. https://doi.org/10.1530/ERC-19-0019
15. Casasent AK, Almekinders MM, Mulder C, Bhattacharjee P, Collyar D, Thompson AM, et al. Learning to distinguish progressive and non-progressive ductal carcinoma in situ. Nat Rev Cancer. 2022;22(12):663-78. https://doi.org/10.1038/s41568-022-00512-y
16. Ward BA, McKhann CF, Ravikumar TS. Ten-year follow-up of breast carcinoma in situ in Connecticut. Arch Surg. 1992;127(12):1392-5. https://doi.org/10.1001/archsurg.1992.01420120026004
17. Nakhlis F, Harrison BT, Giess CS, Lester SC, Hughes KS, Coopey SB, et al. Evaluating the rate of upgrade to invasive breast cancer and/or ductal carcinoma in situ following a core biopsy diagnosis of non-classic lobular carcinoma in situ. Ann Surg Oncol. 2019;26(1):55-61. https://doi.org/10.1245/s10434-018-6937-0
18. Desouki MM, Li Z, Hameed O, Fadare O, Zhao C. Incidental atypical proliferative lesions in reduction mammoplasty specimens: analysis of 2498 cases from 2 tertiary women's health centers. Hum Pathol. 2013;44(9):1877-81. https://doi.org/10.1016/j.humpath.2013.02.015
19. King TA, Pilewskie M, Muhsen S, Patil S, Mautner SK, Park A, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. J Clin Oncol. 2015;33(33):3945-52. https://doi.org/10.1200/JCO.2015.61.4743
20. Scoggins M, Krishnamurthy S, Santiago L, Yang W. Lobular carcinoma in situ of the breast: clinical, radiological, and pathological correlation. Acad Radiol. 2013;20(4):463-70. https://doi.org/10.1016/j.acra.2012.08.020
21. Shamir ER, Chen YY, Chu T, Pekmezci M, Rabban JT, Krings G. Pleomorphic and florid lobular carcinoma in situ variants of the breast: a clinicopathologic study of 85 cases with and without invasive carcinoma from a single academic center. Am J Surg Pathol. 2019;43(3):399-408. https://doi.org/10.1097/PAS.0000000000001191
22. De Brot M, Koslow Mautner S, Muhsen S, Andrade VP, Mamtani A, Murray M, et al. Pleomorphic lobular carcinoma in situ of the breast: a single institution experience with clinical follow-up and centralized pathology review. Breast Cancer Res Treat. 2017;165(2):411-20. https://doi.org/10.1007/s10549-017-4334-1
23. Foote FW, Stewart FW. Lobular carcinoma in situ: a rare form of mammary cancer. Am J Pathol. 1941;17(4):491-6. https://doi.org/10.3322/canjclin.32.4.234
24. Fadare O, Dadmanesh F, Alvarado-Cabrero I, Snyder R, Stephen Mitchell J, Tot T, et al. Lobular intraepithelial neoplasia [lobular carcinoma in situ] with comedo-type necrosis: a clinicopathologic study of 18 cases. Am J Surg Pathol. 2006;30(11):1445-53. https://doi.org/10.1097/01.pas.0000213290.58283.82
25. 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;15(10):1044-50. https://doi.org/10.1097/01.MP.0000027624.08159.19
26. Begg CB, Ostrovnaya I, Carniello JV, Sakr RA, Giri D, Towers R, et al. Clonal relationships between lobular carcinoma in situ and other breast malignancies. Breast Cancer Res. 2016;18(1):66. https://doi.org/10.1186/s13058-016-0727-z
27. Sakr RA, Schizas M, Carniello JV, Ng CK, Piscuoglio S, Giri D, et al. Targeted capture massively parallel sequencing analysis of LCIS and invasive lobular cancer: repertoire of somatic genetic alterations and clonal relationships. Mol Oncol. 2016;10(2):360-70. https://doi.org/10.1016/j.molonc.2015.11.001
28. Harrison BT, Nakhlis F, Dillon DA, Soong TR, Garcia EP, Schnitt SJ, et al. Genomic profiling of pleomorphic and florid lobular carcinoma in situ reveals highly recurrent ERBB2 and ERRB3 alterations. Mod Pathol. 2020;33(7):1287-97. https://doi.org/10.1038/s41379-020-0459-6
29. Page DL, Kidd TE, Dupont WD, Simpson JF, Rogers LW. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. Hum Pathol. 1991;22(12):1232-9. https://doi.org/10.1016/0046-8177(91)90105-x
30. Page DL, Dupont WD, Rogers LW. Ductal involvement by cells of atypical lobular hyperplasia in the breast: a long-term follow-up study of cancer risk. Hum Pathol. 1988;19(2):201-7. https://doi.org/10.1016/s0046-8177(88)80350-2
31. Coopey SB, Mazzola E, Buckley JM, Sharko J, Belli AK, Kim EM, et al. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Breast Cancer Res Treat. 2012;136(3):627-33. https://doi.org/10.1007/s10549-012-2318-8
32. Mooney KL, Bassett LW, Apple SK. Upgrade rates of high-risk breast lesions diagnosed on core needle biopsy: a single-institution experience and literature review. Mod Pathol. 2016;29(12):1471-84. https://doi.org/10.1038/modpathol.2016.127
33. Nakhlis F, Harrison BT, Giess CS, Lester SC, Hughes KS, Coopey SB, et al. Evaluating the rate of upgrade to invasive breast cancer and/or ductal carcinoma in situ following a core biopsy diagnosis of non-classic lobular carcinoma in situ. Ann Surg Oncol. 2019;26(1):55-61. https://doi.org/10.1245/s10434-018-6937-0
34. Abdel-Fatah TM, Powe DG, Hodi Z, Reis-Filho JS, Lee AH, Ellis IO. Morphologic and molecular evolutionary pathways of low nuclear grade invasive breast cancers and their putative precursor lesions: further evidence to support the concept of low nuclear grade breast neoplasia family. Am J Surg Pathol. 2008;32(4):513-23. https://doi.org/10.1097/PAS.0b013e318161d1a5
35. Said SM, Visscher DW, Nassar A, Frank RD, Vierkant RA, Frost MH, et al. Flat epithelial atypia and risk of breast cancer: a mayo cohort study. Cancer. 2015;121(10):1548-55. https://doi.org/10.1002/cncr.29243
36. Dialani V, Venkataraman S, Frieling G, Schnitt SJ, Mehta TS. Does isolated flat epithelial atypia on vacuum-assisted breast core biopsy require surgical excision? Breast J. 2014;20(6):606-14. https://doi.org/10.1111/tbj.12332