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# Surgery for Lobular Carcinoma in Situ: To Do or Not to Do?

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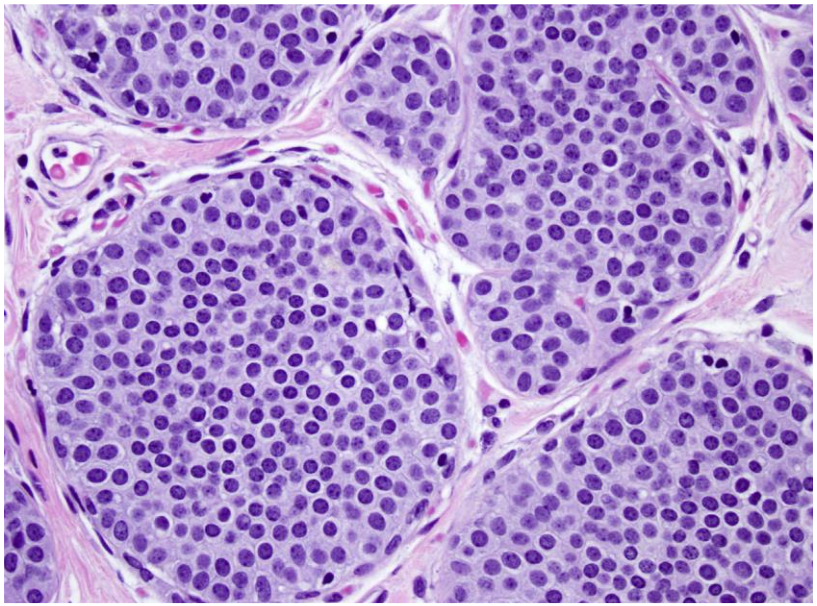
# Disclosure

- Honoraria: Chugai, AstraZeneca, Kyowa Hakko Kirin, and Eisai
- Research grant: Eisai

# Lobular Carcinoma in Situ (LCIS)

- A risk factor and a non-obligate precursor lesion of invasive breast cancer



## CLINICAL FEATURES

- Incidental findings
- Associated with calcifications, or non-mass-like lesions

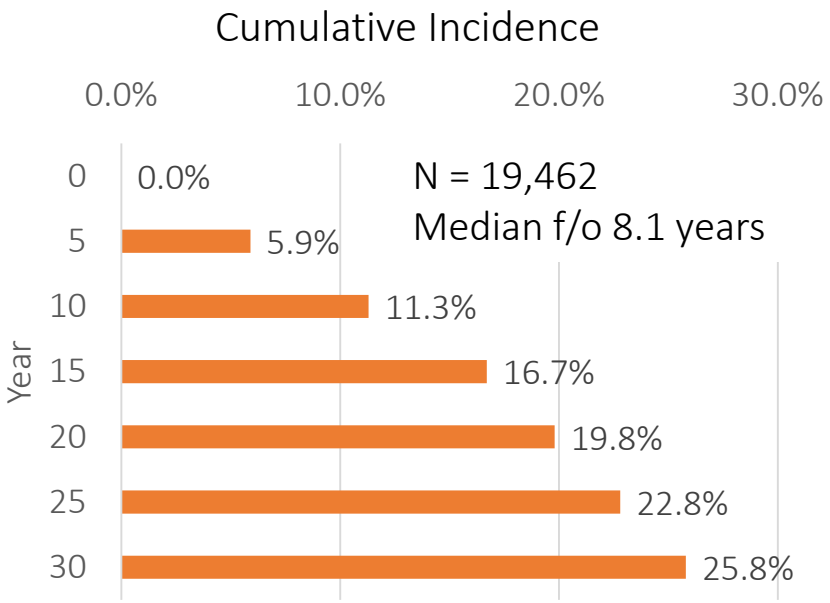
- Multicentric (60-80%)
- Bilateral (20-60%)

(Wen HY, Surg Pathol Clin, 2018)
(Akashi-Tanaka S, Breast Cancer, 2000)

# LCIS as a risk factor

## Annual incidence of subsequent breast cancer

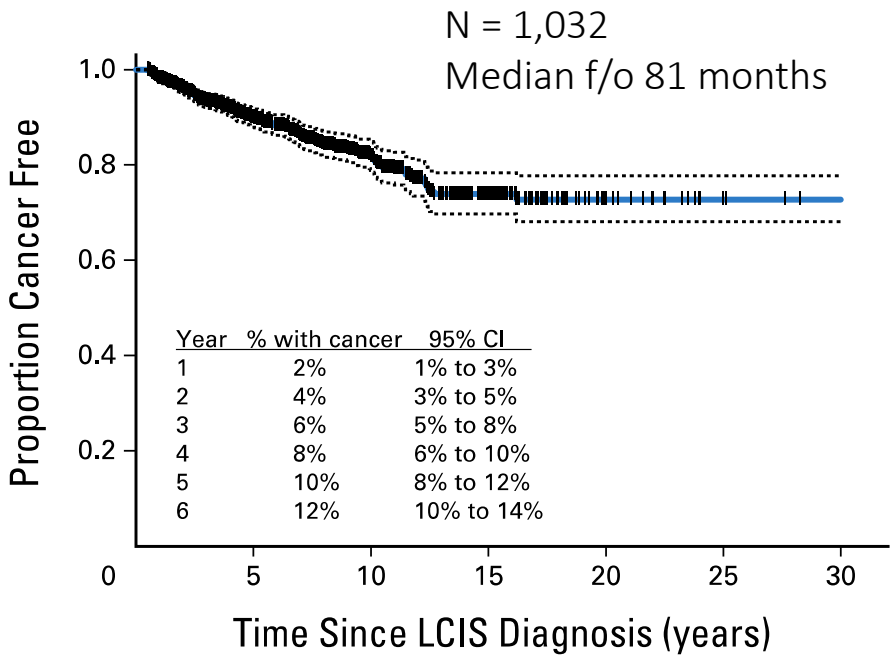
- SEER database




Annual incidence: 1%

(Wong SM, Ann Surg Oncol, 2017)

- MSKCC cohort



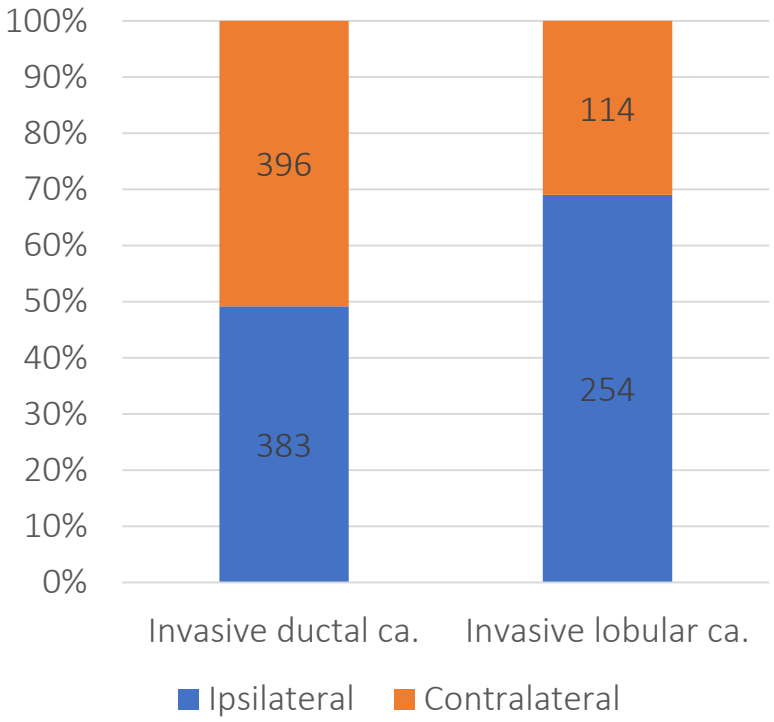

Annual incidence: 2%

(King TA, J Clin Oncol, 2015)

# LCIS as a risk factor

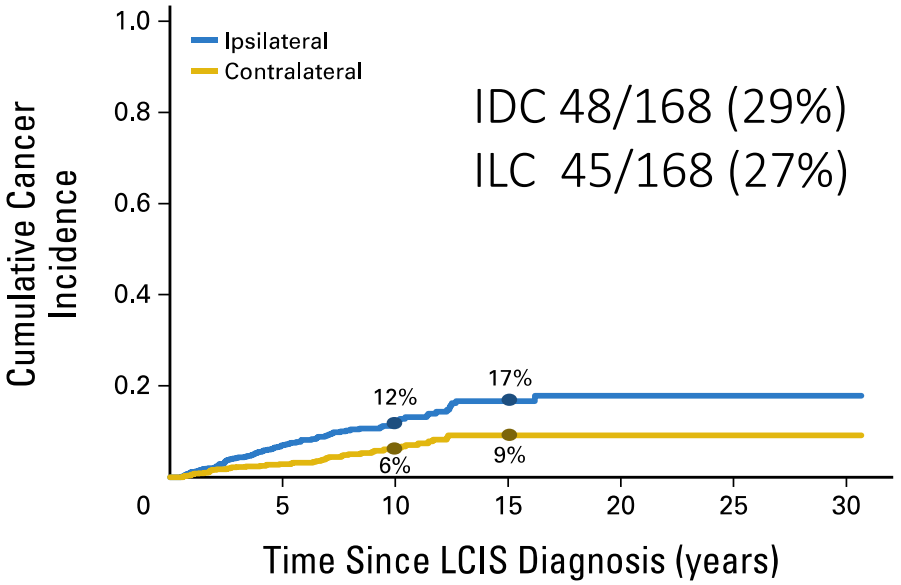
## Characteristics of subsequent breast cancer

- SEER database




(Wong SM, Ann Surg Oncol, 2017)

- MSKCC cohort

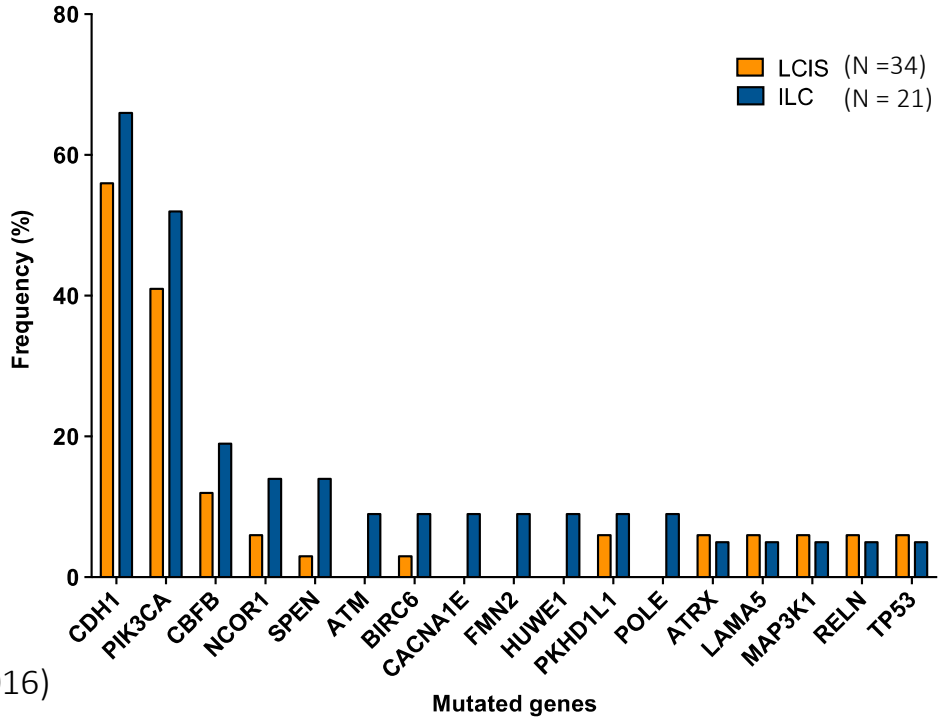



(King TA, J Clin Oncol, 2015)

# LCIS as a non-obligate precursor lesion

## Comparison of the repertoire of somatic mutations in LCIS and ILC

- Targeted capture massively parallel sequencing and whole exome sequencing analyses identified a similar repertoire of somatic mutations in LCIS (N = 34) and ILC (N = 24)
- Pairwise analysis of the 19 synchronous LCIS-ILC paired lesions demonstrated at least one shared mutation in 14 (74%) pairs

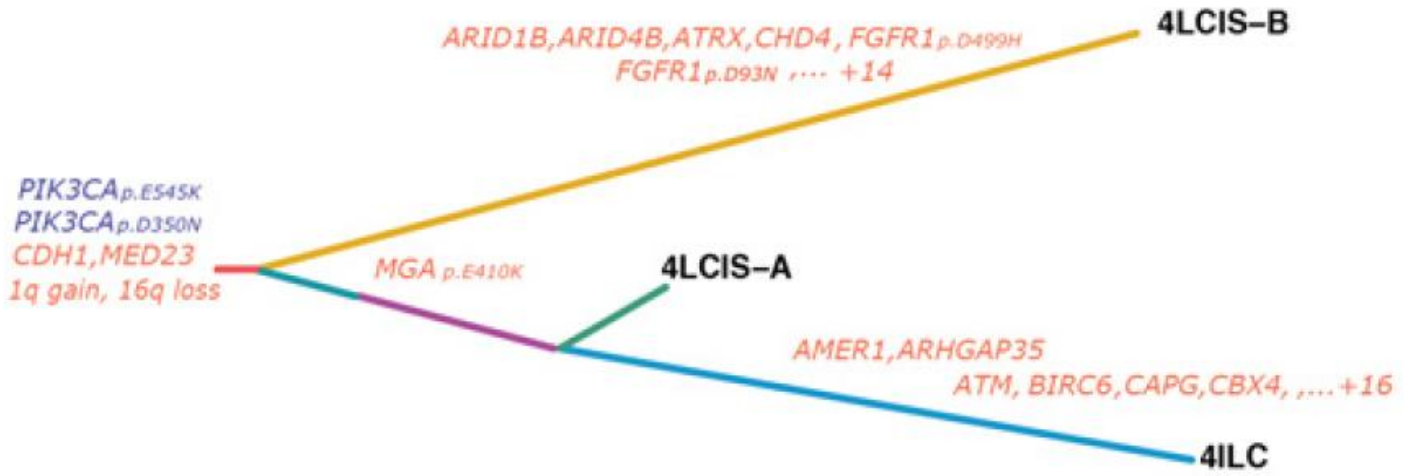



(Sakr RA, Mol Oncol, 2016)

# LCIS as a non-obligate precursor lesion

## Intralesion genetic heterogeneity and clonal evolution in the progression to ILC

- LCIS is a genetically advanced lesion, often displaying intralesion genetic heterogeneity, with minor sub-clones of LCIS becoming the dominant clone in ILCs




(Lee JY, Clin Cancer Res, 2018)

# TNM Staging in AJCC 8th edition

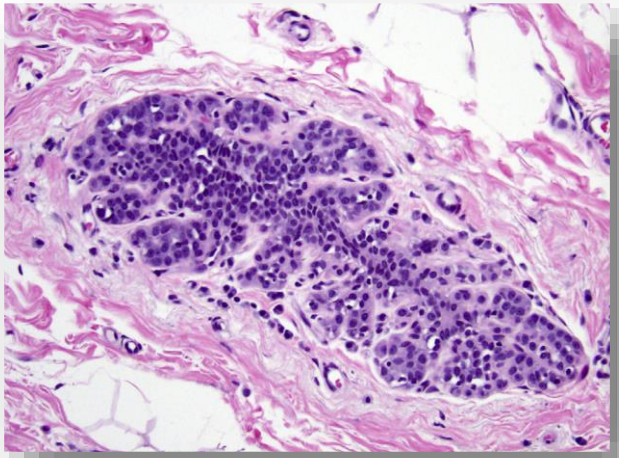
| T CATEGORY | T CRITERIA |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis (DCIS)[a] | Ductal carcinoma in situ (DCIS) |
| Tis (Paget) | Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, but the presence of Paget disease should still be noted. |
| T1 | Tumor ≤ 20 mm in greatest dimension |
| T1mi | Tumor ≤ 1 mm in gre |
| T1a | Tumor > 1 mm but ≤ |
| T1b | Tumor > 5 mm but ≤ |
| T1c | Tumor > 10 mm but ≤ |
| T2 | Tumor > 20 mm but ≤ |
| T3 | Tumor > 50 mm in greatest dimension |
| T4 | Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4 |
| T4a | Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4 |
| T4b | Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma |
| T4c | Both T4a and T4b are present |
| T4d | Inflammatory carcinoma (see "Rules for Classification") |

[a]Lobular carcinoma in situ is a benign entity and is removed from TNM staging in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, eighth edition.

LCIS is removed as a pathologic tumor in situ (pTis) category for T categorization. LCIS is a benign entity and is removed from TNM staging.

(Giuliano AE, CA Cancer J Clin, 2017)

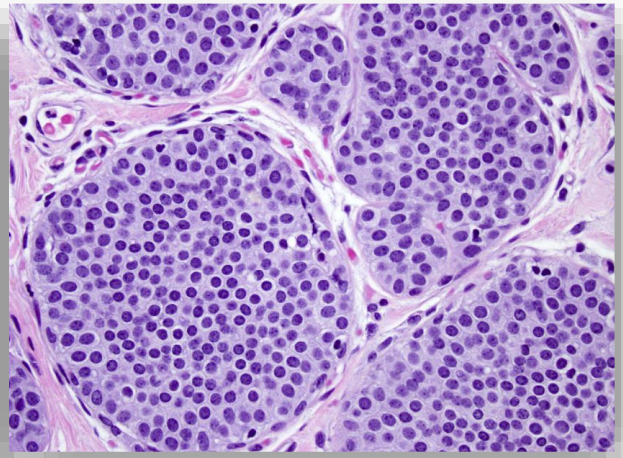
# Lobular Neoplasia



Atypical Lobular Hyperplasia (ALH)

Less than half of acini are distended or distorted by small dyshesive epithelial cells with uniform nuclei

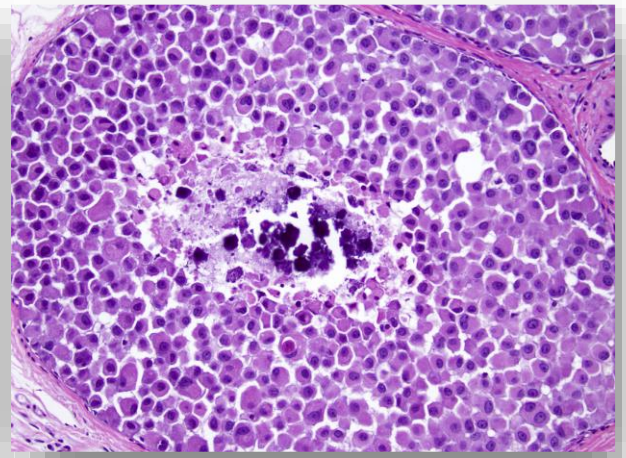
RR 3-6x



Classic LCIS

More than half of acini are distended or distorted by small dyshesive epithelial cells with uniform nuclei

RR 7-11x



Pleomorphic/non-classic LCIS

Cells are more dyshesive, and have more variability in nuclear size and shape than classic LCIS. A comedo necrosis is evident.

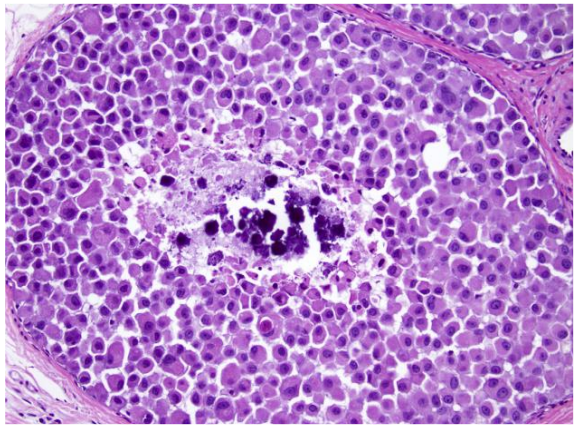
RR ???

(Page DL, Hum Pathol, 1991)
(Wen HY, Surg Pathol Clin, 2018)
(Morrow M, Nat Rev Clin Oncol, 2015)

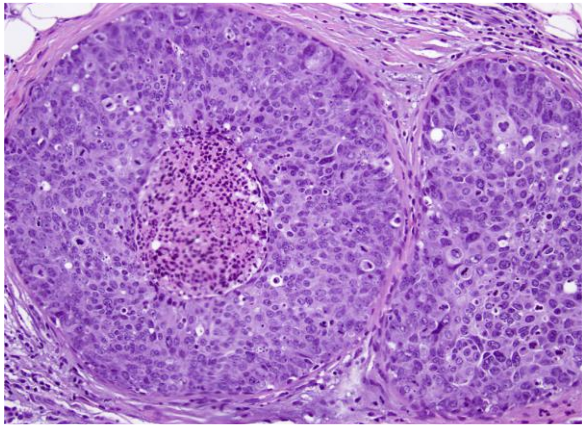
# Pleomorphic/Non-classic LCIS

## Clinical and pathological features

- First described by Frost in 1996
- Women with pleomorphic LCIS are older than classic LCIS
- Often detected by mammography (calcifications, architectural distortion, or mass lesion)
- Pathological presentation (solid growth pattern, nuclear pleomorphism, necrosis, or calcification) closely mimics DCIS



Pleomorphic LCIS



DCIS

(Wen HY, Surg Pathol Clin, 2018)

# Pleomorphic/Non-classic LCIS

## Management of patients diagnosed on core biopsies

- Upgrade rate: mean 39% (range 18-100%)
  - Higher than Classic LCIS (< 3%)
  - No predictive marker for upgrading
- Natural history remains difficult to ascertain
  - Inter-observer variability of pathological diagnosis
  - Limited number of data
  - Some cases have been treated as DCIS
- Surgical excision with negative margin is recommended
- Clinical benefit of radiotherapy is unknown

(NCCN Guidelines)
(Nakhlis F, Ann Surg Oncol, 2019)

# Voting 1

- Should pleomorphic LCIS be pathologically distinguished from classic LCIS or DCIS on core biopsy?
  1. Yes
  2. No
  3. Abstain

# Classic LCIS

## Management of patients diagnosed on core biopsies

- Upgrade rate: 1.0 - 4.4%
  - TBCRC 020 trial (Prospective study)
    - 76 cases with ALH/LCIS diagnosed on core biopsies
    - Cases with discordant imaging were excluded
    - All cases underwent surgical excision
    - 1 case (1%: 95%CI 0.01-7) was upgraded
- Routine excision is not indicated for women with classic LCIS on core biopsy and concordant imaging findings

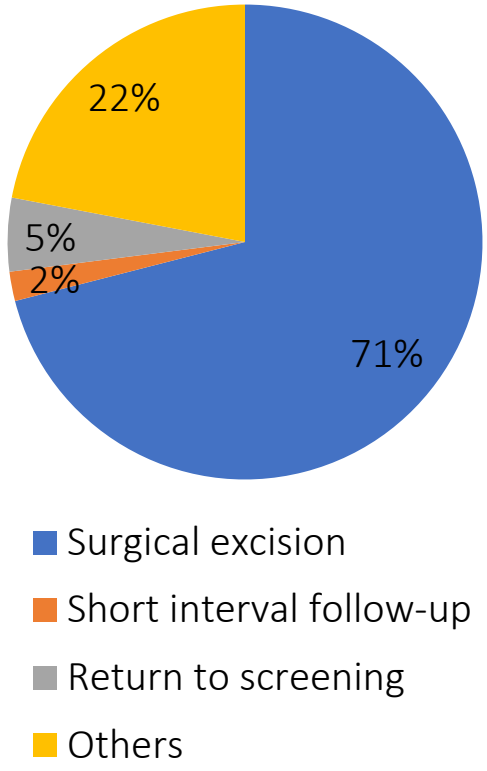
(Wen HY, Surg Pathol Clin, 2018)
(Nakhlis F, Ann Surg Oncol, 2016)
(NCCN Guidelines)

# Classic LCIS

## Management of patients diagnosed on core biopsies

US

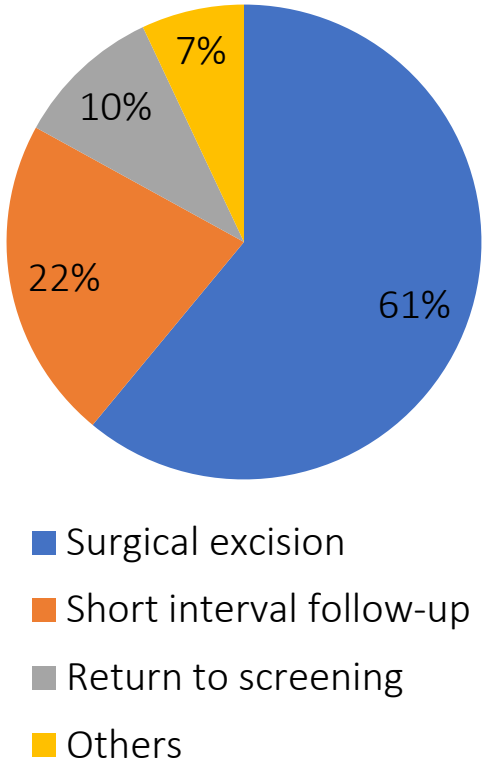
(41 US academic institutions)




(Falomo E, Curr Probl Diagn Radiol, 2018)

UK

(173 UK breast surgeons)




(Chester R, Ann R Coll Surg Engl, 2015)

# Classic LCIS

## Management of patients diagnosed on core biopsies
## Situations in Japan

- In Japan, most breast surgeons follow the NCCN guideline regarding the management of LCIS
- NCCN guideline
  - -2016: Surgical excision was recommended
  - 2017-: Management was divided according to LCIS subtype
  - 2019-: Management of LCIS was removed from “Breast cancer guideline”
- Surgical excision is recommended to most cases with LCIS diagnosed on core biopsy
  - Surveillance without surgical excision is recommended to selected cases

# Voting 2

- Can surgical excision be avoided in women with classic LCIS diagnosed on VAB (concordant with imaging)?
  1. Yes
  2. No
  3. Abstain

# Classic LCIS

## Chemoprevention

- RCTs showed risk reduction of breast cancer
  - NSABP P-1 trial : RR 0.54 (95%CI: 0.27-1.02)
  - NCIC CTG MAP.3 trial: HR 0.61 (95%CI: 0.20-1.82)
- Guidelines recommend that use of chemoprevention should be discussed as an option to reduce the risk of breast cancer

(Fisher B, J Natl Cancer Inst, 2005)
(Goss PE, N Engl J Med, 2011)

(ASCO guideline, 2013)
(NCCN guideline)

# Classic LCIS
## Chemoprevention

- Despite the recommendations, actual rate of chemoprevention uptake remains low (8-30%)
  - Women ≧ 50 years of age were more likely to take chemoprevention
  - Fear of adverse effects was the most common refusal reason
- Low dose TAM (5 mg/d for 3 years) can halve breast cancer events [HR 0.48 (95%CI: 0.26-0.92)] with a limited toxicity

(Flanagan MR, Ann Surg Oncol, 2019)
(Marmor S, Cancer Causes & Control, 2019)
(Trivedi MS, Cancer Prev Res, 2017)
(Hermel DJ, Clin Breast Cancer, 2017)
(Reimers LL, Breast J, 2015)
(DeCensi A, J Clin Oncol, 2019)

# Classic LCIS

## Surveillance

- American Cancer Society Guidelines for Breast Screening with MRI
  - Recommended MRI screening
    - Lifetime risk ~20-25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history
  - Insufficient evidence to recommend for MRI screening
    - LCIS, ALH, or ADH
- A retrospective study at MSKCC
  - N = 776 (MMG 321, MMG+MRI 455)
  - MRI does not result in increased cancer detection rates (short-term), nor does it result in earlier stage at diagnosis

(Saslow D, CA Cancer J Clin 2007)
(King TA, Breast Cancer Res Treat, 2013)

# Voting 3

- Should chemoprevention be presented as an option to all women with LCIS?
  1. Yes
  2. No
  3. Abstain

# LCIS/ILC and germline *CDH1* variants

- Hereditary diffuse gastric cancer (HDGC)
  - An autosomal dominant inherited disease associated of *CDH1* germline variants
  - Lobular breast cancer (LBC) is the second most frequent type of neoplasia
- Recently, novel *CDH1* germline variants were detected in women with LBC without family history for gastric cancer
  - Frequency: 2.9% (14/482)
  - Bilateral LBC or family history of two or more case of LBC (<50 years at onset) is a criterion for *CDH1* testing

(Pharoah PD, Gastroenterology, 2001)
(Corso G, Fam Cancer, 2016)
(van der Post RS, J Med Genet 2015)

# Voting 4

- Should germline *CDH1* testing be made available to women with bilateral LCIS or family history of two or more case of lobular cancer?
  1. Yes
  2. No
  3. Abstain

# Summary

- LCIS is a risk factor and a non-obligate precursor lesion of invasive breast cancer
  - LCIS is a benign entity and is removed from TNM staging
- Surgical excision is recommended to pleomorphic LCIS diagnosed on core biopsy
- Routine excision is not indicated for women with classic LCIS on core biopsy and concordant imaging findings
- Use of chemoprevention should be discussed as an option to reduce the risk of breast cancer
- There are controversy in testing criteria for *CDH1* variants in cases with LCIS