Lobular Carcinoma in Situ During Preoperative Biopsy and the Rate of Upgrade

Jeea Lee

Yonsei University College of Medicine

Ga Yoon Ku

Yonsei University College of Medicine

Haemin Lee

Yonsei University College of Medicine

Hyung Seok Park (✉ imgenius@yuhs.ac)

Yonsei University College of Medicine

Ja Seung Ku

Yonsei University College of Medicine

Jee Ye Kim

Yonsei University College of Medicine

Seho Park

Yonsei University College of Medicine

Seung Il Kim

Yonsei University College of Medicine

Byeong-Woo Park

Yonsei University College of Medicine

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Abstract

Background: There is a potential risk that lobular carcinoma in situ (LCIS) on preoperative biopsy might be diagnosed as ductal carcinoma in situ (DCIS) or invasive carcinoma in the final pathology. This study aimed to evaluate the rate of upgrade of LCIS on preoperative biopsy to DCIS or invasive carcinoma.

Methods: Data of 55 patients with LCIS on preoperative biopsy were analyzed. All patients underwent surgery between 1991 and 2016 at Severance Hospital in Seoul, Korea. We analyzed the rate of upgrade of preoperative LCIS to DCIS or invasive cancer in the final pathology. The clinicopathologic features related to the upgrade were evaluated.

Results: The rate of upgrade of LCIS to DCIS or invasive carcinoma was 16.4% (9/55). In multivariate analysis, microcalcification and progesterone receptor expression were significantly associated with the upgrade of LCIS ($P = 0.023$ and 0.044 , respectively).

Conclusions: The current study showed a relatively high rate of upgrade of LCIS on preoperative biopsy to DCIS or invasive cancer. The presence of microcalcification and progesterone receptor expression may be potential predictors of upgradation of LCIS on preoperative biopsy. Surgical excision of the LCIS during preoperative biopsy could be a management option to identify the concealed malignancy.

Background

Traditionally, an excision is recommended for patients with lobular carcinoma in situ (LCIS) diagnosed on core needle biopsy [1]. However, the management of LCIS has been controversial, and some authors advocate observation rather than surgical excision [2, 3].

LCIS was excluded from the malignant category in the 8th American Joint Committee on Cancer (AJCC) staging system for breast cancer [4]. The National Comprehensive Cancer Network (NCCN) guidelines® recommend active surveillance, surgical excision, and/or other interventions such as counseling for lifestyle modification, medication, or surgery for reducing the risk of breast cancer in patients with LCIS diagnosed on core needle biopsy [1]. Surgical excision should be considered only in patients with pleomorphic LCIS or lesions that are non-concordant with imaging findings [1]. Patients with classic LCIS and those with lesions that are concordant with imaging findings can be followed up with close observation [1].

Across the literature, the upgrade rates of LCIS on core needle biopsy to invasive carcinoma or ductal carcinoma in situ (DCIS) at surgical excision have been reported from 0–50% [5]. Previous studies have shown that the upgrade rate varies, and there is still no consensus about surgical treatment or observation in cases of LCIS [5].

In this study, we analyzed the upgrade rate and risk factors associated with the upgrade of LCIS diagnosed at preoperative biopsy and performed surgical excision in a single institution.

Methods

We reviewed electronic medical records (EMR) and data from the Breast Cancer Registry database of Severance Hospital, Yonsei University Health System, and conducted a retrospective study. The computerized medical database included information about the clinical, radiological, and pathological characteristics of patients; treatment methods; preoperative and postoperative pathologic findings; preoperative findings on physical examination, mammography, and ultrasonography; recurrence and mortality; and follow-up data, as previously described [6]. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (4-2020-0716).

We reviewed the data of 80 patients who underwent breast surgery for LCIS at Severance Hospital between January 1991 and December 2016 using EMRs and data from the database. We excluded patients diagnosed with invasive cancer at preoperative biopsy ($n = 6$) and non-LCIS at preoperative biopsy ($n = 18$); we also excluded one case involving unavailable data. Finally, 55 cases of LCIS diagnosed at preoperative biopsy were enrolled in the study (Fig. 1).

The patients underwent breast-conserving surgery or mastectomy, according to the patients' and surgeons' preferences based on the tumor size, location, and multiplicity of tumors. After surgery, some patients who underwent breast-conserving surgery received adjuvant radiotherapy according to the multidisciplinary team approach.

Patient characteristics such as age, clinical findings, preoperative biopsy methods, pathological findings, and treatment methods were reviewed. A preoperative physical examination was performed by experienced surgeons, and a palpable mass was described in the medical database with or without information about the location or size of the lesion. Preoperative imaging evaluations including mammography, ultrasonography, and magnetic resonance imaging (MRI) were performed. The initial reports of preoperative imaging studies were reviewed for their correlation with the final pathology.

Final pathology records were reviewed to analyze histopathological variables including tumor size, hormone receptor status, E-cadherin expression, pleomorphism, and comedo necrosis. Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER) 2/neu expression were evaluated on formalin-fixed, paraffin-embedded whole sections of the surgically resected breast specimens using immunohistochemistry (IHC). The cutoff value for ER and PR positivity was $> 1\%$ staining on IHC. Pleomorphism and comedo necrosis were reviewed by an experienced breast pathologist, JSK, and categorized as either absent or present.

Statistical analysis

Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the Student's t-test or Mann-Whitney U test. Univariate and multivariate analyses for calculating the odds ratios of significant risk factors for the upgrade of preoperative LCIS were performed using binary logistic regression. Multivariate analysis was adjusted for age, microcalcification on

mammography, and PR status as covariates. Risk factors were selected using backward stepwise regression based on the probability of the likelihood ratio. A $P < 0.05$ was considered significant; all tests were two-sided. Statistical analyses were conducted using a commercially available statistical software SPSS Statistics 25 (IBM Corp., Armonk, NY, USA).

Results

Overall, 55 cases of preoperative LCIS were identified. They were classified into two different groups based on the final pathology: 9 cases of postoperative DCIS or invasive carcinoma in the upgrade group and 46 cases of postoperative LCIS in the non-upgrade group (Fig. 1). The upgrade rate of preoperative LCIS to DCIS or invasive carcinoma was 16.4% (9/55) (Fig. 2a).

Clinicopathologic features were compared between the upgrade group and the non-upgrade group (Table 1). There was no significant difference between the two groups in terms of age; physical examination findings; ultrasonographic findings; Breast Imaging-Reporting and Data System (BI-RADS) category; MRI findings; biopsy methods; surgical methods; tumor site; tumor size; and the status of ER, PR, HER-2, and E-cadherin expression at baseline. Microcalcification on mammography was seen in 41.3% (19/46) of patients in the non-upgrade group and in 77.8% (7/9) of patients in the upgrade group, which indicated a marginally significant difference ($P = 0.05$). In the multivariate analysis, microcalcification on mammography and PR positivity were significantly associated with the risk of upgrade of preoperative LCIS (Odds ratio [OR] = 14.155; $P = 0.023$ and OR = 10.621; $P = 0.044$) (Table 2).

Table 1
Comparison of clinicopathologic features between the upgrade group and non-upgrade group

	Preoperative LCIS (<i>n</i> = 55)		<i>P</i> value
	Upgrade group	Non-upgrade group	
	(<i>n</i> = 9, 16.4%) number (%)	(<i>n</i> = 46, 83.6%) number (%)	
Age (years)			0.467
≤50	4 (44.4%)	28 (60.9%)	
>50	5 (55.6%)	18 (39.1%)	
Physical exam			> 0.999
Non-palpable	7 (77.8%)	36 (78.3%)	
Palpable	2 (22.2%)	10 (21.7%)	
Microcalcification on mammography			0.050
Negative	1 (11.1%)	24 (52.2%)	
Positive	7 (77.8%)	19 (41.3%)	
Unknown	1 (11.1%)	3 (6.5%)	
USG mass			> 0.999
Negative	6 (66.7%)	28 (63.6%)	
Positive	3 (33.3%)	16 (36.4%)	
BI-RADS category			0.767
Category 4	8 (88.9%)	34 (73.9%)	
Category 5	0 (0%)	2 (4.3%)	
Others (category 2,3,6)	1 (11.1%)	10 (21.7%)	
MRI enhancement			0.649
Negative	1 (16.7%)	12 (32.4%)	
Positive	5 (83.3%)	25 (67.6%)	
Biopsy methods			> 0.999
* Weak positive			
<i>BI-RADS</i> Breast Imaging-Reporting and Data System, <i>ER</i> estrogen receptor, <i>HER</i> human epidermal growth factor receptor, <i>LCIS</i> lobular carcinoma in situ, <i>MRI</i> magnetic resonance imaging, <i>PR</i> progesterone receptor, <i>USG</i> ultrasonography			

Core needle biopsy	5 (55.6%)	31 (67.4%)	
Vacuum assisted biopsy	4 (44.4%)	12 (26.1%)	
Excisional biopsy	0 (0%)	3 (6.5%)	
Surgery type			> 0.999
Partial mastectomy	7 (77.8%)	36 (78.3%)	
Total mastectomy	2 (22.2%)	10 (21.7%)	
Tumor site			0.475
Left	6 (66.7%)	23 (50.0%)	
Right	3 (33.3%)	23 (50.0%)	
Tumor size			> 0.999
≤ 2 cm	7 (77.8%)	30 (75.0%)	
> 2 cm	2 (22.2%)	10 (25.0%)	
ER			> 0.999
Negative	0 (0%)	1 (2.3%)	
Positive	9 (100.0%)	42 (97.7%)	
PR			0.241
Negative	1 (11.1%)	16 (38.1%)	
Positive	8 (88.9%)	26 (61.9%)	
HER-2			0.796
0 ~ 1+	5 (55.6%)	21 (45.7%)	
2+	2 (22.2%)	17 (37.0%)	
3+	2 (22.2%)	4 (8.7%)	
E-cadherin expression			0.327
Negative	9 (100.0%)	38 (82.6%)	
Positive*	0 (0%)	1 (2.2%)	
Not done	0 (0%)	7 (15.2%)	
* Weak positive			
<i>BI-RADS</i> Breast Imaging-Reporting and Data System, <i>ER</i> estrogen receptor, <i>HER</i> human epidermal growth factor receptor, <i>LCIS</i> lobular carcinoma in situ, <i>MRI</i> magnetic resonance imaging, <i>PR</i> progesterone receptor, <i>USG</i> ultrasonography			

Table 2
Univariate and multivariate analysis for the upgradation of preoperative LCIS ($n = 55$)

Clinicopathologic factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
Age (≤ 50 years vs. >50 years)	1.944 (0.460–8.223)	0.366	-	
Microcalcification on MMG (negative vs. positive)	8.842 (1.000-78.221)	0.050	14.155 (1.448-138.394)	0.023
PR (negative vs. positive)	4.923 (0.562–43.123)	0.150	10.621 (1.069-105.559)	0.044
<i>MMG</i> mammography, <i>PR</i> progesterone receptor				

Pleomorphism of LCIS was analyzed by preoperative biopsy (Table 3). The rates of pleomorphic LCIS and comedo necrosis were 19.5% and 17.1%, respectively. Based on preoperative biopsy findings, there were no cases of pleomorphic LCIS in the upgrade group, whereas there were 8 cases of pleomorphic LCIS in the non-upgrade group. There were only 7 cases of comedo necrosis in the non-upgrade group. There were no significant differences between the two groups in terms of pleomorphism and comedo necrosis ($P = 0.318$ and 0.310 , respectively).

Table 3
Pleomorphic subtypes and comedo necrosis in the upgrade and non-upgrade groups

	Preoperative LCIS ($n = 55$)*		
	Upgrade group ($n = 9$)	Non-upgrade group ($n = 46$)	P
	number (%)	number (%)	value
Preop - Pleomorphic type			0.318
No	8 (100%)	25 (75.8%)	
Yes	0	8 (24.2%)	
Preop – comedo necrosis			0.310
No	8 (100%)	26 (78.8%)	
Yes	0	7 (21.2%)	
* Missing data were excluded from the analysis (preop-pleomorphic $n = 14$, preop-comedo necrosis $n = 14$)			

Discussion

The current study demonstrated that the upgrade rate of preoperative LCIS was 16.4%. A relatively significant proportion of the patients with preoperative LCIS had hidden invasive cancer that might be missed if only core needle biopsy is used as a definitive diagnostic tool. A previous study reported an 8.4–9.3% rate of upgrade for LCIS, which was considerably higher than the acceptable target for surveillance, and the authors suggested excision of preoperative LCIS confirmed by a core needle biopsy [5]. Li et al. suggested that LCIS might be a precursor of invasive carcinoma, and localized treatment for LCIS is warranted [7]. Cheng et al. also suggested that lumpectomy is the most appropriate management for LCIS [8]. In this study, all upgrade groups were diagnosed by core needle or vacuum assisted biopsy, not by excisional biopsy (Fig. 2b). This result suggested that excision could be considered in case of LCIS for reliable tissue confirmation.

Nevertheless, there is controversy about the treatment of LCIS diagnosed on core needle biopsy, because of the varying upgrade rates mentioned in the literature (Table 4). Schmidt et al. reported that the true upgrade rate of LCIS was 4% on excluding pleomorphic LCIS and image-discordant lesions [9]. They suggested that surgery for classic LCIS is unnecessary, and careful radio-pathological correlation during initial biopsy is critical. Wen and Brogi suggested that classic LCIS on core needle biopsy with concordant imaging does not require surgical resection [10]. However, our study showed a relatively high rate of upgrade of LCIS, regardless of the presence of pleomorphism. There was no association between the upgrade rate and presence of pleomorphic LCIS or comedo necrosis in this study. Even though the pathologic slides of all cases of LCIS were reviewed by a specialized pathologist, no pleomorphism or comedo necrosis was detected in the upgrade group. Pleomorphic LCIS is considered to be an aggressive type of LCIS associated with high-grade DCIS and invasive cancer [11, 12]. In the previous studies, the upgrade rates of pleomorphic LCIS were relatively high, at 20–100% [9, 13, 14]. Hence, the NCCN guidelines recommend surgical excision for pleomorphic LCIS [1]. The difference in the upgrade rate of pleomorphic LCIS between the previous and current study might be due to the small sample size of each study and inter-observer variability in the pathological evaluations.

Table 4
Upgrade rates of lobular neoplasia or LCIS during the recent 5 years

Authors	Years	Pathology	N	Upgrade rate	Features
Benjamin C. Calhoun [12]	2016	LN	76	13%	Included pLCIS as an upgraded pathology
Thaer Khoury [13]	2016	LN	63	24%	MRI-guided core biopsy
		LCIS	34	32%	
				67% (pLCIS)	
Schmidt H [9]	2018	LN	115	11% (all LN)	Observation vs. excision
				4% (except pLCIS and discordant lesions)	
Desai AA [14]	2018	pLCIS	15	20%	
Iskender Sinan Genco [18]	2019	LN	287	3.8%	Classic LN diagnosed on breast core needle biopsy
		cLCIS	115	7%	
Holbrook AI [19]	2019	LN	66	7.6%	
Nakhli F [20]	2019	NC-LCIS	76	36%	Supporting routine excision
<i>LCIS</i> lobular carcinoma in situ, <i>LN</i> lobular neoplasia, <i>NC-LCIS</i> non-classic lobular carcinoma in situ, <i>pLCIS</i> pleomorphic lobular carcinoma in situ					

The definition of concordant images and pathologic results is variable [15]. Youk et al. summarized five categories of radio-pathological correlation in a sonography-guided core needle biopsy of a breast lesion: concordant malignancy, discordant malignancy, concordant benign, discordant benign, and borderline or high-risk [15]. Before the AJCC system 8th edition was published, LCIS was considered a malignant lesion; thus, when core needle biopsy for a BI-RADS category 4a lesion reveals classic LCIS, it could be considered either as discordant benign or borderline. When the radio-pathological correlation is borderline, a multidisciplinary approach or surgical excision to identify the hidden malignancy could be adopted. However, after the AJCC system 8th edition was published, when core needle biopsy for a category 4a lesion revealed classic LCIS, it was considered as concordant benign and not borderline or high-risk. In such cases, surgical excision should not be routinely recommended according to the NCCN guidelines. Since most previous studies used data obtained before the AJCC system 8th edition was published, the definition of the radio-pathological correlation for classic LCIS was considered to be either discordant benign or borderline. When we reviewed a previous study, the exact definition of the radio-pathological correlation was not specified [16, 17]. Since the general recommendation of close follow-up for classic LCIS is based on ambiguous or arbitrary definition of the radio-pathological correlation for classic LCIS, it is difficult to routinely follow the revised guidelines for classic LCIS. A more detailed definition of the

radio-pathological correlation for LCIS should be developed to avoid miscommunication among physicians, radiologists, pathologists, and surgeons.

The current study found that microcalcification on mammography and the expression of PR were significant in predicting the likelihood of upgrade of LCIS. A previous study reported a similar association between the upgrade rate of LCIS and mammographic calcification [5]. This result was similar to that observed in our study. Therefore, when cases of LCIS diagnosed on preoperative biopsy involve mammographic microcalcification and PR positivity, hidden invasive cancer or DCIS might be discovered after surgical excision (Fig. 3).

There were some limitations to this study. First, we analyzed a small number of cases. Few cases of preoperative LCIS were evaluated for calculating the upgrade rate. Second, when we reviewed the pathologic data, including data on pleomorphism, there were some missing data that might have affected the accuracy of the analysis. In the future, more large-scale, long-term research on LCIS is necessary. Finally, our research has the limitations of a retrospective study. Nevertheless, the current study has valuable implications for clinical practice. Our study focused only on LCIS and not on lobular neoplasia or atypical lobular hyperplasia. We found that the ambiguity in the definition of radio-pathological correlation in the previous studies might have weakened the evidence of the current guidelines. In the current study, multivariate analysis found two significant predictors of the upgrade of preoperative LCIS.

Conclusions

This study showed a relatively high rate of upgrade to DCIS or invasive cancer in cases of preoperative LCIS. The presence of microcalcification on mammography and PRs can be potential predictors of upgrade. Surgical excision of LCIS during core needle biopsy could be considered as a management option to identify a hidden malignancy.

Abbreviations

AJCC: American Joint Committee on Cancer

BI-RADS: Breast Imaging-Reporting and Data System

DCIS: Ductal carcinoma in situ

EMR: Electronic medical records

ER: Estrogen receptor

HER: Human epidermal growth factor receptor

IHC: Immunohistochemistry

LCIS: Lobular carcinoma in situ

MRI: Magnetic resonance imaging

NCCN: National Comprehensive Cancer Network

OR: Odds ratio

PR: Progesterone receptor

Declarations

Ethics approval

This retrospective chart review study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (4-2020-0716).

Consent to participate

Not applicable

Consent to publication

Not applicable

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors have no conflict of interest.

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No funding was received for this study.

Author Contributions

HSP conceived and designed the study. HSP, JL, GYK and HML analyzed and interpreted data, wrote the paper with input from all authors. JSK contributed to the interpretation of the pathology. All authors contributed to revise the article and approved the submitted version.

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Figures

Figure 1

Schema of the study design to analyze the upgrade rate of preoperative LCIS

Figure 2

The rate of upgrade of preoperative LCIS (n = 55) (a) The rate of upgrade of preoperative LCIS (b) The rate of upgrade of preoperative LCIS according to the methods of preoperative biopsy Bx biopsy, CNB core needle biopsy, LCIS lobular carcinoma in situ, VAB vacuum assisted-biopsy

Figure 3

A case of the upgrade group with definite microcalcification on mammography without USG and MRI findings and the PR positivity (a) Increased extent and amount of grouped microcalcification in lower

central portion of the left breast on mammography (b) Multiple probable benign enhancement without localized suspicious enhancements in both breasts on MRI (c) Increased benign looking lesions in the both breasts on USG LCIS lobular carcinoma in situ, MRI magnetic resonance imaging, PR progesterone receptor, USG ultrasonography