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ORIGINAL ARTICLE – BREAST ONCOLOGY

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

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ABSTRACT

Background. A diagnosis of *non-classic* lobular carcinoma in situ (NC-LCIS) encompasses a variety of lesions with poorly characterized natural history. We evaluated upgrade rates and factors associated with upgrade to malignancy following a core biopsy diagnosis of NC-LCIS, and its natural history.

Methods. Upon Institutional Review Board approval, pathology databases were searched for NC-LCIS core biopsy diagnoses (carcinoma in situ [CIS], CIS with ductal and lobular features [CIS/DLF], pleomorphic LCIS [P-LCIS], variant LCIS [V-LCIS], LCIS with necrosis). Cases with available core and excision pathology were included, while cases with concurrent ipsilateral invasive carcinoma (IC), ductal carcinoma in situ (DCIS), and/or atypical ductal hyperplasia were excluded.

Results. Overall, 121 NC-LCIS cases were identified from 1998 to 2017. We excluded 46 cases with concurrent cancer; 75 patients with 76 NC-LCIS core biopsy diagnoses followed by excision formed our study cohort. Median age was 56 years (range 41–83), and all imaging findings were classified as Breast Imaging Reporting and Data System 4; calcifications were the most common biopsy indication (80%). Excision yielded malignancy in 27 (36%) patients (IC 17, 63%; DCIS alone 10, 37%). We were unable to identify radiologic or pathologic features predictive of upgrade. Of 49 pure NC-LCIS cases, 15 (31%) had mastectomy, 9 (18%) had excision and radiation, and 25 (51%) had excision alone. At a median follow-up of 58 months (range 1–224), 1/25 (4%) patients with excision alone developed ipsilateral DCIS 14 months later.

Conclusions. In this series of NC-LCIS, 36% of cases were upgraded, supporting routine excision. We were unable to identify predictors of upgrade. Among 25 patients with pure NC-LCIS, only one patient developed a future ipsilateral cancer. Further study of the natural history of NC-LCIS is warranted.

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According to the World Health Organization (WHO), classic lobular carcinoma in situ (LCIS) consists of a monomorphic population of dyshesive cells with small uniform round nuclei, and scant cytoplasm.[1] The cells can have mild to moderate nuclear variability. The WHO describes only two variants of LCIS: classic LCIS with central comedo necrosis and pleomorphic LCIS (marked nuclear pleomorphism equivalent to high-grade ductal carcinoma in situ [DCIS], with or without apocrine features, and with or without comedo necrosis). However, pathologists encounter other types of LCIS that do not clearly fit into these categories, and have used variable terminology to describe them.

'Non-classic LCIS' can be used as a general term to describe lesions that have features of LCIS but fall outside the definition of classic LCIS. These lesions may exhibit 'higher-grade' features, such as comedonecrosis with or without nuclear pleomorphism.[1–5] The first description of NC-LCIS was reported by Frost et al. in 1996, who noted 'pleomorphic LCIS' (P-LCIS) associated with invasive

pleomorphic lobular carcinoma.[6] Subsequently, in 2002, Sneige et al. reported isolated P-LCIS, referring to this unusual lesion as 'pleomorphic lobular (ductal-lobular) carcinoma in situ', introducing a variation in terminology to classify these lesions as early as their first description.[7] Since then, a number of additional terms have been utilized to describe NC-LCIS and its morphologic variations, such as pleomorphic apocrine LCIS, LCIS with pleomorphic features, large cell LCIS, signet cell LCIS, and LCIS with comedonecrosis.

These lesions appear to be biologically distinct from classic LCIS, yet they present a challenge due to their rarity and lack of consistency in terminology used by pathologists to refer to them,[8] resulting in a paucity of data describing the natural history of the various forms of NC-LCIS to inform clinical decision making. Furthermore, an additional obstacle in studying NC-LCIS is that historically these lesions were likely frequently classified as DCIS,[9] as highlighted by Sullivan et al., who reported that among 75 cases signed out as solid DCIS, E-cadherin staining demonstrated 9 (12%) to be of the lobular phenotype,[9] illustrating that retrospective identification of NC-LCIS cases in institutional and population databases can be difficult.

As for the significance of an NC-LCIS diagnosis on core biopsy, the existing literature documents upgrade rates ranging from 25 to 80%; however, the number of reported cases are quite small, with the largest series having 25 patients.[10–18] The goals of our study were to evaluate the rate of upgrade to invasive breast carcinoma and/or DCIS following excision of NC-LCIS diagnosed on core biopsy, to identify clinical, pathologic and/or imaging features of NC-LCIS associated with an upgrade in diagnosis, and to evaluate the natural history of NC-LCIS after a negative surgical excision.

METHODS

Upon obtaining approval from the Dana Farber/Harvard Cancer Center Institutional Review Board, we performed a search of the participating institutions' pathology databases (Brigham and Women's Hospital, Boston, MA, USA; Massachusetts General Hospital, Boston, MA, USA) to identify cases with NC-LCIS diagnosis on breast core biopsy from 1998 to 2017. The search keywords and phrases included the following: carcinoma in situ (CIS), carcinoma in situ with ductal and lobular features (CIS/DLF), variant lobular carcinoma in situ (V-LCIS), pleomorphic lobular carcinoma in situ (P-LCIS), and lobular carcinoma in situ with necrosis. These search criteria were chosen as these were the terms known to have been used in clinical pathology reports to describe NC-LCIS at the participating institutions over the time period selected. Only cases of NC-LCIS on core biopsy that had been subject to internal review by the breast pathology services at the respective institutions, and with available pathology reports from subsequent surgical excision, were included. Upgrade was defined as the diagnosis of invasive carcinoma and/or DCIS documented at subsequent surgical excision; all other diagnoses at excision, including atypical ductal hyperplasia (ADH) and classic LCIS, were considered not upgraded. Cases of NC-LCIS on core biopsy with a concurrent ipsilateral invasive breast cancer and/or DCIS diagnoses, as well as with ADH in the same core biopsy, were excluded.

Patient demographics, presenting characteristics, pathology findings from the core biopsy and subsequent surgical excision and clinical outcomes were obtained from the medical records. For 59 cases with available radiographic materials, pertinent breast imaging studies were independently reviewed by an author with specialty in breast imaging (CSG) blinded to histopathologic excision results. For the remaining 17 cases, breast imaging results were extracted from the medical record.

Descriptive statistics were used to summarize clinical, imaging, and pathologic findings associated with the diagnosis of NC-LCIS on core biopsy followed by excision.

RESULTS

We identified 121 cases with a core biopsy diagnosis of NC-LCIS reviewed at Brigham and Women's Hospital and/or Massachusetts General Hospital and subject to surgical excision between 1998 and 2017. Among these cases, 46 had an associated diagnosis of ADH, DCIS, or invasive carcinoma and were subsequently excluded, leaving 75 eligible patients. One patient had concurrent bilateral diagnoses of NC-LCIS, thus 76 core biopsies with NC-LCIS formed the final study cohort (Fig. 1).

Patient demographics and presenting characteristics are described in Table 1. Median patient age was 56 years (range 41–83); 52 patients (68%) were postmenopausal and, of these, 7 (13%) had used hormone replacement therapy. Mammographic breast density, as stated in the imaging report and/or issued upon central review by a dedicated breast imager (CSG), was classified as 'heterogeneously dense' in 41 patients (70%) and 'extremely dense' in 2 patients (3%) among the 59 cases with breast imaging materials available for review.

In 68 of 76 (89%) cases, the imaging modality that prompted the core biopsy demonstrating NC-LCIS was screening mammography; the remaining 8 cases were

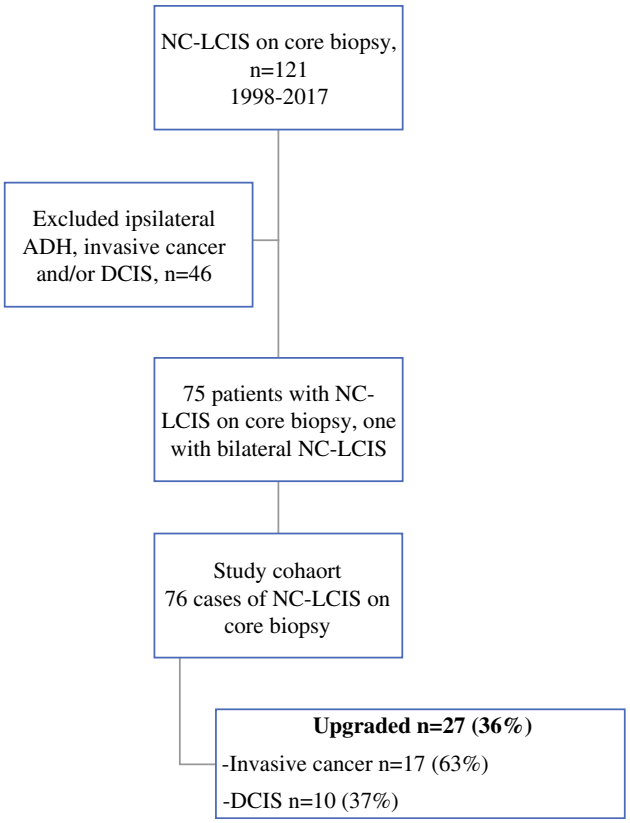

FIG. 1 Study selection process. *NC-LCIS* non-classic lobular carcinoma in situ, *DCIS* ductal carcinoma in situ, *ADH* atypical ductal hyperplasia

detected by screening breast magnetic resonance imaging. The most common imaging abnormality was mammographic calcifications (n = 61, 80% of the entire cohort).

Core Biopsy Diagnoses

The term most commonly used to refer to NC-LCIS on core biopsy was CIS/DLF (n = 37, 49%), followed by CIS (n = 19, 25%), V-LCIS (n = 16, 21%), and P-LCIS (n = 4, 5%). The majority of the lesions were E-cadherin-negative (40 of 51 tested, 78%) and estrogen receptor (ER)-positive (46 of 51 tested, 90%); 30/49 (61%) were progesterone receptor (PR)-positive, and, of 35 cases in which human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) was obtained, only 6 (17%) were positive.

Surgical Procedures and Pathology Findings at Excision

Among 75 patients in this cohort, 4 (5%) went straight to mastectomy following the NC-LCIS core biopsy diagnosis, one of whom was upgraded to DCIS, and, among the remaining 71 patients, there were 72 (95%) surgical excisions. Overall, 27 of the total 76 cases (36%) were upgraded to invasive carcinoma and/or DCIS after surgery; 33 demonstrated only additional NC-LCIS (43%), and, in 16 cases (21%), there was no residual NC-LCIS.

Among the 27 upgraded cases, 17 (63%) were upgraded to invasive carcinoma with or without DCIS, and the remaining 10 patients had pure DCIS. Nine of 17 (53%) invasive cancers were lobular cancers and 5 (29%) were invasive ductal; 3 (18%) showed mixed invasive ductal and lobular histology. The median invasive cancer size was 0.2 cm (range 0.06–1.1 cm); two patients had microinvasive carcinoma only (0.06 cm and 0.1 cm, respectively). Six invasive cancers (35%) were histologic grade 1, seven (41%) were grade 2, two (12%) were grade 3, and in the remaining two invasive cancers grade was not reported. The majority of invasive cancers were ER-positive (n = 15, 88%) or PR-positive (n = 11, 65%), and only one (6%) was HER2-positive. All invasive cancers lacked lymphovascular invasion. One patient had a node-positive carcinoma. This was a 54-year-old woman with a 0.7 cm area of mammographic calcifications found to have CIS/DLF on stereotactic biopsy; subsequent excision revealed a 0.4 cm grade 2 invasive lobular carcinoma, ER- and PR-positive and HER2-negative. Follow-up sentinel node biopsy revealed 0.3 cm of metastatic carcinoma in one of two sentinel nodes.

The details regarding the upgrade to malignancy for specific NC-LCIS subtypes, as stated in the original pathology reports, are provided in Table 2. An upgrade in diagnosis was found in 4 of 19 (21%) CIS lesions, 4 of 16 (25%) V-LCIS lesions, 16 of 37 (43%) CIS/DLF lesions, and 3 of 4 (75%) P-LCIS lesions.

When comparing presenting clinicopathologic and imaging characteristics of NC-LCIS associated with an upgrade, we were not able to identify any statistically significant differences to propose possible predictors of upgrade (Table 1). Additionally, when specifically evaluating the terminology used to describe NC-LCIS on core biopsy as a potential predictor of an upgrade, no such association was observed (Table 2).

Independent Pathology Review of Core Biopsies

Although all 76 cases had been previously reviewed as part of clinical care, only 40 had core biopsy materials currently available for independent pathology review by two coauthors (BH, SL) with a dedicated interest in breast pathology. Review reclassified 25 (63%) cases as P-LCIS, 3 cases as ‘florid LCIS with necrosis’, one as ‘variant LCIS with histiocytoid features’ and one as borderline P-LCIS (i.e. intermediate rather than high nuclear grade). Additionally, in one case, P-LCIS was seen in conjunction with DCIS, and, in another case, P-LCIS was seen in conjunction with severe ADH, neither of which had been

TABLE 1 Presenting clinical, imaging, and pathologic characteristics of 76 diagnoses of NC-LCIS in 75 patients, median age 56 years (range 41–83)

Demographics and breast cancer risk modifiers		NC-LCIS		
Variable	All	Upgraded (n = 27, 36%)	Not upgraded (n = 49, 64%)	p value[a]
Postmenopausal	52 (68)	20 (74)	32 (65)	0.61
Prior contralateral breast cancer	4 (5)	2 (7)	0	0.12
Prior ipsilateral ALH and/or classic LCIS	3 (4)	1 (4)	2 (4)	1
Prior contralateral ALH and/or classic LCIS	1 (1)	1 (4)	0	0.36
Presenting imaging findings				
Detected by screening mammography	68 (89)	23 (85)	45 (92)	0.44
Mammographic calcifications	61 (80)	20 (74)	41 (84)	0.37
Detected by screening MRI	8 (11)	4 (15)	4 (8)	0.44
Immunohistochemistry of NC-LCIS on core biopsy				
E-cadherin-positive[b]	5/51 (10)	2/18 (11)	3/33 (9)	1
E-cadherin-negative	40/51 (78)	15/18 (83)	25/33(76)	0.73
ER-positive	46/51 (90)	14/17(82)	32/34 (94)	0.32
PR-positive	30/49 (61)	7/15 (47)	23/34 (68)	0.21
HER2-positive	6/35 (17)	3/12 (25)	3/23 (13)	0.39
HER2-negative	20/35 (57)	6/12 (50)	14/23 (61)	0.72

Data are expressed as n (%) or n/N (%)

ALH atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ, *MRI* magnetic resonance imaging, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *NC-LCIS* non-classic lobular carcinoma in situ, *CIS/DLF* carcinoma in situ with ductal and lobular features, *CIS* carcinoma in situ, *V-LCIS* variant lobular carcinoma in situ

[a]Fisher's exact test

[b]Among the five NC-LCIS cases that were E-cadherin-positive on core biopsy, three were CIS/DLF, one was CIS, and one was V-LCIS

TABLE 2 Terminology used for NC-LCIS on core biopsy and subsequent upgrade on excision[a]

Variable	Upgraded (n = 27)	Not upgraded (n = 49)	p value[b]
CIS	4 (15)	15 (31)	0.17
CIS/DLF	16 (59)	21 (43)	0.23
P-LCIS	3 (11)	1 (2)	0.13
V-LCIS	4 (15)	12 (24)	0.39

Data are expressed as n (%)

CIS carcinoma in situ, *CIS/DLF* carcinoma in situ with ductal and lobular features, *P-LCIS* pleomorphic lobular carcinoma in situ, *V-LCIS* variant lobular carcinoma in situ, *DCIS* ductal carcinoma in situ

[a]The cases upgraded to pure DCIS were as follows: 1 of 4 (25%) upgraded CIS cases, 7 of 16 (44%) upgraded CIS/DLF cases, 1 of 3 (33%) upgraded P-LCIS cases, and 1 of 4 (25%) upgraded V-LCIS cases

[b]Fisher's exact test

previously described in the original pathology report. Finally, one core biopsy failed to demonstrate NC-LCIS (atypical lobular hyperplasia only), and, in one case, DCIS could not be excluded (Table 3).

Local Management, Systemic Therapy, and Follow-Up

Among the 49 patients without an upgrade, 15 (31%) underwent mastectomy, none of which were referred to as risk-reducing procedures in the medical records, nor were any of these performed in conjunction with a contralateral prophylactic mastectomy (CPM). Twenty-five (51%) patients had excision alone and 9 (18%) patients had excision and adjuvant radiation therapy. Seven (14%) patients received chemoprevention. All patients who had an excision with or without radiation had negative margins (defined as $\geq$ 0.2 cm). Among 27 patients with an upgrade in diagnosis, 14 (52%) underwent mastectomy, two of which (14%) were accompanied by CPM.

At a median follow-up of 58 months (range 1–224 months), one patient experienced an ipsilateral breast cancer (DCIS) 14 months after excision alone for the diagnosis of CIS/DLF on core biopsy excised to negative margins. The initial CIS/DLF diagnosis and the recurrent DCIS were located in the same quadrant of the affected breast.

TABLE 3 Original diagnosis and independent review of core biopsy materials (available in 40 cases)

Original diagnosis	Review diagnosis				
	P-LCIS (n = 25)	Florid LCIS (n = 3)	Variant LCIS with histiocytoid features (n = 1)	P-LCIS and DCIS (n = 2)	Borderline, other (n = 9)
CIS (n = 10)	4	1	0	1	4
CIS/DLF (n = 19)	17	0	0	1	1
P-LCIS (n = 0)	–	–	–	–	–
V-LCIS (n = 11)	4	2	1	0	4

Data are expressed as no. of cases

CIS carcinoma in situ, *CIS/DLF* carcinoma in situ with ductal and lobular features, *P-LCIS* pleomorphic lobular carcinoma in situ, *V-LCIS* variant lobular carcinoma in situ, *LCIS* lobular carcinoma in situ, *DCIS* ductal carcinoma in situ

DISCUSSION

In this series, we evaluated our cancer center experience with breast core biopsies demonstrating NC-LCIS and found that the upgrade rate to invasive breast carcinoma and/or DCIS in these patients was 36%. This is consistent with the existing literature addressing this issue (Table 4).[9–18] Most published series utilize the term 'pleomorphic LCIS' (P-LCIS), with patient numbers ranging from 4 to 23, and reported upgrade rates ranging from 18 to 100%.[9–16,18] The second most commonly used term is 'variant LCIS' (V-LCIS), having up to 15 patients in published series and upgrade rates on excision reported in up to 27%.[9,17] In our report, we included these two diagnostic terms as well as the diagnoses 'CIS' and 'CIS/DLF', and report upgrade rates ranging from 21% (CIS) to 75% (P-LCIS).

Recognizing the lack of consensus on terminology and interobserver variability with respect to classification of NC-LCIS, our data suggest, even among cases classified at a single institution, current terminology is not sufficient to identify cases of NC-LCIS that are associated with upgrade rates low enough to support omission of excisional biopsy. Upon independent pathology review, which was possible for 40 core biopsies, 25 (63%) were classified as P-LCIS.

TABLE 4 Review of the published literature addressing upgrade to invasive carcinoma and/or DCIS on excision of NC-LCIS on core biopsy

References	NC-LCIS subtype	No. of excisions	No. of upgrades (%)
Georgian-Smith and Lawton[10]	P-LCIS	5	2 (40)
Lavoue et al.[11]	P-LCIS	10	3 (33)
Chivukula et al.[12]	PLCIS	12	3 (25)
Carder et al.[13]	P-LCIS	8	2 (25)
Sullivan et al.[9]	V-LCIS	11	4 (36)
	P-LCIS	17	3 (18)
Niell et al.[14]	P-LCIS	4	4 (100)
Meroni et al.[15]	P-LCIS	12	6 (50)
Flanagan et al.[16]	P-LCIS	21	11 (52)
Susnik et al.[17]	V-LCIS	15	4 (27)
Guo et al.[18]	P-LCIS	23	14 (60)
This report	CIS	19	4 (21)
	CIS/DLF	37	16 (43)
	V-LCIS	16	4 (25)
	P-LCIS	4	3 (75)
Total		214	83 (39)

CIS carcinoma in situ, *CIS/DLF* carcinoma in situ with ductal and lobular features, *P-LCIS* pleomorphic lobular carcinoma in situ, *V-LCIS* variant lobular carcinoma in situ, *DCIS* ductal carcinoma in situ, *NC-LCIS* non-classic lobular carcinoma in situ

This is an important observation of a previous divergence in terminology being potentially amenable to convergence with use of a single term in the majority of cases.

Additionally, we were unable to identify any differences in imaging findings among NC-LCIS cases that were upgraded versus those that were found to represent pure in situ lesions. Admittedly, the lack of statistically significant differences is possibly a reflection of this study's small sample size. Nevertheless, in the absence of reliable presenting factors associated with a low risk of upgrade, routine excision of NC-LCIS on core biopsy is warranted.

The retrospective nature of this study, as well as institution-specific tendencies for the use of particular terminology, represent additional limitations. Furthermore, it is conceivable that the lesions described as 'carcinoma in situ with ductal and lobular features' may not have been universally perceived by surgeons and pathologists as NC-LCIS but rather as DCIS. Historically, NC-LCIS lesions have not been consistently classified and there is a significant amount of interobserver variability in diagnosis and management,[8] with some pathologists defaulting to the diagnosis of DCIS and/or clinicians assuming that they are dealing with DCIS. To this point, in this series we observed that among 49 patients in whom there was not an upgrade in diagnosis, 24 (49%) received local therapy that would have been recommended for an overt carcinoma, including 15 patients (31%) who underwent a mastectomy and 9 patients (18%) who received adjuvant radiation therapy. This finding illustrates the uncertainty associated with clinical decision making regarding NC-LCIS. Unfortunately, the paucity of data often results in more aggressive local treatment strategies, despite the fact that data regarding subsequent risk of breast cancer are limited. As such, it is impossible to estimate the benefit of mastectomy or the effectiveness of radiation therapy.

The natural history of pure NC-LCIS remains difficult to ascertain. In our series, among 49 pure cases, 25 were treated with excision alone, and, at median follow-up of 58 months, 1 patient (4%) was diagnosed with a subsequent ipsilateral DCIS. Other studies containing follow-up information for pure P-LCIS, include small series of 5–31 patients, and have reported a wide range of subsequent ipsilateral malignancy, from 0 to 57%.[7,16,19–21] De Brot et al. reported on seven P-LCIS patients with a longer median follow-up of 67 months, four of whom (57%) developed ipsilateral breast cancers (one DCIS, two invasive lobular carcinomas, and one invasive ductal carcinoma).[20] In a similar study by Khoury et al., among 31 P-LCIS patients only 4 (13%) developed ipsilateral carcinomas at a median follow-up of 56 months.[21] Finally, there are also at least three studies that report no subsequent ipsilateral cancer events, with mean follow-up ranging between 17 months and 4.1 years.[7,16,19] Thus, with limited numbers and a wide range of events, the true increased future breast cancer risk imparted by a diagnosis of NC-LCIS remains unknown. Furthermore, only some of the available reports describe the use of chemoprevention,[19–21] with its receipt ranging between 14 and 38%, despite the fact that the majority of these lesions in our study and others demonstrate ER positivity.[19,20,22]

CONCLUSIONS

We report a 36% upgrade rate to invasive breast carcinoma and/or DCIS on excision of 76 NC-LCIS cases diagnosed by core biopsy supporting the practice of routine excision. This finding is consistent with prior reports, yet represents the largest single-institution series. Despite central review of pathology and imaging studies, we were unable to identify presenting clinicopathologic factors associated with an upgrade on excision. Additionally, we found that among 25 patients with pure NC-LCIS treated with excision alone, the incidence of future ipsilateral malignancy was low (4%); however, among the published literature, there is significant variability in reported rates of subsequent ipsilateral cancers following a diagnosis of NC-LCIS. Larger studies evaluating the natural history of NC-LCIS are needed to ensure appropriate clinical care for these patients.

DISCLOSURES None.

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