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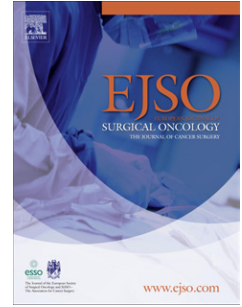
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Dear Editor,

We are submitting the article “Management of Lobular Neoplasia in Situ and Atypical Lobular Hyperplasia – A Review” to your auspicious journal with your kind permission. We have made an effort in an attempt to address the management controversies surrounding lobular Neoplasia on reviewing the currently available literature and have made some management recommendations based on the evidence available.

We have also declared no funding and no conflict of interest on the authors’ form.

Whilst, I (Mubashar Hussain) remain the first author for the paper, Mr G Cunnick could be kindly contacted for correspondence.

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Thank you.

Sincerely,

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Abstract:

Objectives: To determine the incidence of malignancy (invasive carcinoma or DCIS) in patients diagnosed with lobular neoplasia (B3) on core needle biopsy (CNB) of breast lesions by reviewing the published literature.

Methods: Medline, Embase, OVID-database and reference lists were searched to identify and review all English-language articles addressing the management of LN diagnosed on CNB. Studies on mixed breast pathologies were excluded.

Results: Of 1229 LN diagnosed on CNB, 789 (64%) underwent surgical excision. 211 (27%) of excisions contained either DCIS or invasive disease. 280 of the excision specimens were classified as ALH, 241 as LCIS, 22 as pleomorphic LCIS and 246 unspecified LN on the original CNB. After surgical excision, 19% of the ALH cases, 32% of the LCIS cases and 41% of the PLCIS cases, contained malignancy. 29% of the unspecified LNs were upgraded to malignancy. The higher incidence of malignancy within excision specimens for LCIS and PLCIS compared to ALH was significant ($P < 0.04$, < 0.003 respectively).

Conclusion: There is a significant under-estimation of malignancy in patients diagnosed with breast LN on CNB. 27% cases of CNB-diagnosed LN were found to contain malignancy following surgical excision. All patients diagnosed with LN on CNB should be considered for surgical excision biopsy.

Key words: lobular neoplasia; lobular carcinoma in-situ; atypical lobular hyperplasia; pleomorphic lobular carcinoma in-situ; core needle biopsy; e-cadherin.

INTRODUCTION:**Definition**

Ewing [1] was the first to document in-situ lobular neoplasia of the breast in 1919. In 1941, Foote and Stewart [2] characterised lobular neoplasia as a monomorphic population of cells that originates from, fill and distend the terminal ducto-lobular unit and spread in a pagetoid manner between the surface epithelial cells and the basement membrane of the ductal system. The term lobular neoplasia (LN) was introduced in 1978 by Haagenson et al [3], to differentiate it from DCIS, and was described as being a risk indicator for the subsequent development of breast cancer [3,4] rather than a true precursor. They advocated a conservative approach in treating the condition. Lobular proliferation was described as lobular intraepithelial neoplasia with various degrees of atypia (LIN1, LIN2 and LIN3) [5].

Subtypes

ALH and LCIS are now considered to be different entities. Both are characterised by proliferative changes [3] within the terminal duct-lobular units of poorly cohesive, monotonous cuboidal or polygonal cells with clear cytoplasm. The epithelial cells are larger than normal and may contain clear vacuoles called magenta bodies. Intracytoplasmic lumina may be present with infrequent mitotic figures. Although the acini of terminal duct-lobular units are more generally involved, the ducts are also affected [3]. The distinction between ALH and LCIS is based on the degree of involvement of the acini [4, 7, 8], but there may be intra- and inter-observer variability [9]. For a diagnosis of LCIS, more than half the acini must be filled and

distended by the characteristic cells, called type-A cells, leaving no central lumina [10] (figure-1). For ALH, less than half of the acini are affected.

Pleomorphic LCIS (PLCIS) has been described as a more aggressive subtype [11-13] along the spectrum of LN; ranging from ALH to LCIS, to LCIS with type-B cells (i.e. with larger nuclei and increased nuclear-pleomorphism) and finally PLCIS. The distinction between these conditions may be challenging, hence they are often considered together under the umbrella term, 'lobular neoplasia' [3,14]. The cells in PLCIS show more marked pleomorphism with approximately four-times larger nuclei than in LCIS [10]. PLCIS is frequently associated with microcalcifications and central necrosis [11,15,16], which makes the distinction from high-grade DCIS difficult [11,16]. Other variants are endocrine, apocrine, histiocytoid and signet ring LN [17].

Incidence

The true incidence of LN is unknown. The SEER database reports it as 3.19 per 100,000 women [26]; Other studies demonstrate a range from 0.8 to 3.8% on open surgical biopsies and 0.02% to 3.3% on CNB [24,25]. Moreover, LN is found in 5% of all cancer excision specimens [27,28]. The incidence of LN has increased four-fold over the last 20-years [26] and is predicted to increase further [14,35]. This is due to an increased awareness of the condition by histopathologists, the use of vacuum-assisted biopsy devices and other improvements in screening programmes [14,35].

Molecular pathology

The hallmark molecular feature of LN is the loss of E-cadherin [36-38], manifested by immunonegativity for E-cadherin. This is an adhesion molecule, localised at Zonula-adherens of epithelial cells [39,40]. Analyses of E-cadherin truncating mutations have shown similar genetic mutations in LCIS when co-existing with invasive lobular carcinoma. This suggests that they came from the same family and LCIS may have been the predisposing lesion [38]. Classical LN is typically EGFR-1 and HER2-negative [41,42], ER and PR-positive [43]. However, the pleomorphic variants can be ER and PR-negative and HER2-positive [44]. Moreover, PLCIS show similar impairments to those seen in DCIS such as partial chromosome deletions or the acquisition of oncogenes such as c-myc [12]. Cytogenic studies have shown a loss of 16q and gain of 1p for lobular carcinomas which resemble grade I ductal carcinoma [45,46].

Radio-pathological correlation

LN is not typically associated with any specific clinical abnormality. Early studies suggested that classical LN lacks any diagnostic mammographic features [47]. Radio-pathological concordance is important in the management of patients who undergo CNB, because women who have discordant results have traditionally been recommended to undergo a second CNB or surgical excision. Some series showed that repeat biopsy was recommended in 9-58% lesions due to radio-pathological discordance [48-51]. However, PLCIS may be identified on mammography by the presence of microcalcifications [16]. More recent studies have also shown an association between classical LN and microcalcifications. The latter have been reported in up to 88% of cases (ranging 8%-88%) of classical LN diagnosed on CNB

[52-58]. Furthermore, LN could be associated with various mammographic abnormalities, suspicious microcalcifications being the commonest, followed by masses with calcifications, masses alone and architectural distortion [55,57-60]. There was one case of LCIS reported as a faint mammographic mass with a solid nodule on ultrasound [61].

The recognition of discordance is more difficult for masses than for calcified lesions because of the lack of a reliable marker to confirm lesion retrieval [60]. Thus, repeat biopsy or even excision of a mass after the initial LN diagnosis on CNB [48] would be advisable. Still, one is more likely to miss a diagnosis of co-existing breast cancer when microcalcifications are core biopsied when compared to masses [62,63].

Clinical implications

Previously, LCIS was often treated with mastectomy [2,18,19]; while others advocated bilateral mastectomy based on an equal risk of invasive carcinoma in both breasts [20,21]. However, the cumulative risk after the diagnosis of LCIS for ipsilateral invasive carcinoma is 18% and 14% for contralateral, of which 40% are lobular and 60% ductal carcinomas [22]. Such information has led to a shift away from mastectomy towards more conservative management [14]. Thus LN became considered a 'non-obligate precursor' for breast cancer in both breasts, rather than a true precursor [23]. At present, many surgeons do not excise areas of LN diagnosed on CNB, although many patients are followed-up with regular mammography.

OBJECTIVES

The purpose of this review was to determine the incidence of associated invasive breast carcinoma or DCIS in subsequent excision specimens following the initial diagnosis of LN on CNB and to identify the optimum oncological management.

METHODS

The review was facilitated by utilising Medline, Embase, OVID databases, using the search terms ‘lobular carcinoma in-situ’, ‘atypical lobular hyperplasia’, ‘pleomorphic lobular carcinoma in-situ’, ‘lobular neoplasia’, ‘core needle biopsy’ and ‘breast cancer’. Only articles published in the English language were included. Studies on mixed breast pathologies diagnosed on CNB were excluded.

RESULTS (See Tables 1-6)

This analysis was based on pooled data from various studies, involving 1229 patients diagnosed with LN on CNB. 789 had surgical excision. Of the cases of LN which underwent excision, 280 were classified as ALH, 241 as LCIS, 22 as PLCIS and 246 as unspecified LN on the CNB. 211 cases of malignancy (27%) were identified following excision (See Table 1). The incidence for ALH, LCIS, PLCIS and unspecified LN was 19%, 32%, 41% and 29%, respectively. The higher incidence of co-existing malignancy for LCIS and PLCIS when compared to ALH was significant ($P < 0.04$, < 0.003 respectively, Mann-Whitney U-test) but comparison to unspecified LN was not significant. Given the potential bias between smaller and larger studies, and the older and more recent papers, we compared the incidence of malignancy

within these groups. A significant difference was found between the smaller and larger studies - i.e. group-I (<20 cases/study) = 8% (29/348) Vs group-II (\geq 20 cases/study) = 26% (182/689), $P > 0.01$, using Fisher's test. However, no significant difference was observed between the older and more recent studies - i.e. group-I (1999-2003) = 27% (93/348) Vs Group-II (2004-2008) = 26% (118/462), $P > 0.23$, using Chi square and Fisher's test.

DISCUSSION

Risk factors for malignancy

The average age for the diagnosis of LN is between 44 and 47 years. It is 12 times commoner in white than black patients [31]. LN may be multifocal in 50% of cases [29] and carries a bilateral risk for invasive carcinoma in 30% [30,32,34,77,78]. Compared with the general population, the lifetime relative risk of subsequent breast cancer is 11 and 5 for LCIS and ALH, respectively [32-34]. The relative risk for ALH in the presence of a family history for breast cancer is 8 [32]. Some suggest that LN may be a precursor of invasive carcinoma [72,79]. Others suggest it should be considered as an intermediate step in the development of invasive carcinoma, similar to the progression from ADH to DCIS [57,58]. However, the biological significance of LN remains uncertain despite consistent evidence of a high association of LN with malignancy. It is included among the "lesions of uncertain malignant potential – B3", by UK pathologists [80]. Others have demonstrated that LCIS and ALH are not different entities, but are part of a continuum of changes at molecular and cytological levels [2,72,79,81]. The association of LN and malignancy prompted Houssami [66,67] to suggest the current classification for B3 lesions [80,82] be divided into two subgroups based on the risks they pose - i.e. B3 lesions with a lower probability of

cancer, such as radial scars, papillary lesions and phyllodes tumours; and B3 lesions with a higher probability of cancer, such as ADH and LN.

Underestimation of malignancy

The true association of LN with cancer and its management remains controversial [64,65]. However, there is mounting evidence available that there is a significant and consistent risk of underestimating malignancy after LN diagnosis on CNB [57,58,60,66,71] which ranges from 0% to 50% [68]. Newman reported in 1966 that “residual (and possibly antecedent) LCIS was found in 72 of 73 cases with invasive lobular carcinoma” on histopathological examination [69]. More recently, Houssami et al [66,67] reported the underestimation for malignancy of 61% on excision. Londero et al [58] reported an incidence of malignancy in 46% after excision which was even higher for LCIS alone (60%). Lee et al [70] reported that LN diagnosed on CNB is the most frequently upgraded of all B3 lesions to malignancy. Elsheikh and Silverman [57] reported excision biopsies for LN involving 33 patients diagnosed with a mammotome CNB. 18 patients were observed prospectively. 4/13 cases of LCIS revealed invasive cancer. 5/20 cases of ALH revealed DCIS (4 cases) and ILC (1 case). The overall cancer underestimation was 27%. Lechner et al. [71] reported that 34% of LCIS and 21% of ALH cases were associated with malignancy at subsequent excision. The variation of malignancy after excision is probably due to variations in the histopathological diagnosis of LN [55, 68]. Page et al [72] reported 50 of 252 ALH-cases treated by excision subsequently developed invasive breast cancer; of which 12 were contralateral. They suggested a model of premalignancy for ALH, intermediate between a local precursor and a generalised risk for both breasts. The overall underestimation of co-existing malignancy in the current study for LN

diagnosed on CNB was 27% on subsequent surgical excision (Tables 1, 6). Interestingly, there was no significant difference for identification of malignancies on comparing two groups based on publication years of the contributing studies. However, there was a significant difference between the two groups based on number of cases per study. Many of the smaller studies were biased by the fact that many patients were treated conservatively, rather than undergoing surgical excision.

Conservative approach

Some authors have previously suggested a conservative approach following a diagnosis of LN on CNB with annual examinations and mammographic surveillance [28,35,55,75,76]. Their conclusions are based on small retrospective studies. Bauer et al [75] observed only 13 women with a CNB diagnosis of LN of whom 3 were lost to follow-up and 3 did not undergo excision biopsy. One of the remaining 7 cases contained invasive cancer on excision biopsy. Renshaw et al [76] reported 71 cases of LCIS or ALH on CNB. Only 15 cases underwent subsequent excision biopsy of which none contained carcinoma. Berg et al [55] identified 25 cases of LN diagnosed on CNB. 15 of these underwent subsequent excision biopsy. There were 3 cases of ADH and 1 case of DCIS on final histopathology. The authors felt that surgery was not justified, although follow-up was only 2.5 years. Clearly, any underlying DCIS would take much longer to become clinically apparent. Liberman et al [35] reported 14 cases of LCIS and ALH on CNB which underwent subsequent excision. 5 cases also contained radial scars or ADH and 4 cases contained DCIS. 5 cases were pure ALH or LCIS of which none were found to have cancer after excision.

Surgical management

Some early studies reported a lower risk of malignancy with LN (8%), similar to that of papillary lesions and radial scars [52,70,83,84]. Traditionally, these lesions have been managed by surgical excision [85,86], whereas LN has mostly been managed non-operatively. Surgery has also become the standard treatment for ADH diagnosed on CNB, since 25% of cases are associated with malignancy [89].

Nevertheless, many authors [8,15,33,53,54,56-58,70,71,73,74,87] now recommend surgical excision in all patients diagnosed with LN on CNB based on the significant cancer risk. Others recommend certain criteria for surgical excision after the diagnosis of LN which varies from centre to centre due to a lack of prospective studies. Some authors [24,88] advocated that the finding of diffuse LN on CNB (involving multiple ducts or lobules) warrants surgical excision as it cannot be fully analysed by CNB [55]. Others suggested surgical excision for mammographic masses and distortions [35,53,55,57]; which represent clinico-pathological discordance [61]. Excision was also recommended if the histopathological features of LN overlapped with those of DCIS or was difficult to differentiate with E-cadherin immunohistochemistry [13,35,98]. The malignancy risk in such cases is similar to that of ADH alone at CNB [96,97]. Berg et al [55] recommended surgical excision for suspicious microcalcifications on CNB, as there is high risk of co-existing ADH or DCIS. Microcalcifications could be found both in and around cancer in 35% and only in adjacent tissues in 16% of cases [93,55]. Similarly, malignancy may be found in a biopsy for benign-looking calcification [94]. However, breast cancer could still be missed when all of the abnormal mammographic calcifications are retrieved after CNB [57,95,96].

The high incidence of malignancy on subsequent excision observed in this study would justify the decision to offer excision to all patients following the diagnosis of LN on CNB. The risk of malignancy is highest for PLCIS, and lowest for ALH as shown in this study (Tables 1-6). This decision to operate should be made in a multidisciplinary setting and be carefully explained to the patient since majority will be benign.

Pleomorphic variant

PLCIS has a higher association with invasive lobular carcinoma (40-60%), both on CNB and surgical excision [15,16,53]. Therefore, PLCIS appears to be a precancerous lesion and risk factor and carries a worse prognosis. It mandates surgical excision with tumour-free resection margins [13,53]. It should be managed along the same lines as DCIS because of the morphological similarity to high-grade DCIS [86].

Biopsy devices

The use of 11-gauge vacuum-assisted biopsy achieves a lower frequency of radio-pathological discordance [50,99-101]. The tissue volume sampled is five-times greater than with a 14-gauge biopsy gun [102]. This increases the chances of retrieving adjacent lesions for histopathological examination and achieves a higher rate of complete excision of the mammographic target [63,103,104] which improves diagnostic accuracy [101].

Adjuvant therapy

Given that many surgeons have not excised LN diagnosed on CNB, there is limited evidence available for adjuvant therapies. Nevertheless, Fisher et al recommended the routine use of tamoxifen in the management of LCIS (118). However, there is no data to support this approach, especially when one considers that tamoxifen is not routinely recommended for DCIS. Cutuli et al [65] suggested that adjuvant radiotherapy should represent an alternative treatment rather than breast conserving therapy alone or mastectomy. However, no control arm was included and some patients also received tamoxifen. Sasson [107] reported an increased incidence of ipsilateral local recurrence in patients with LCIS mixed with invasive cancer (29% vs 6%), when compared to those without LCIS. All underwent breast conservation and radiotherapy. However, the difference in local recurrence rates may be due to variable use of adjuvant therapy. Others observed no difference in overall survival or local recurrence after 10-years [109] and some authors have demonstrated that the presence of LCIS with the invasive tumour had no correlation with either ipsilateral or contralateral breast cancer [105,106]. LCIS at the margins following breast conservation does not require re-excision [105,107,108].

Limitations

The authors acknowledge that the data for this review originate from different protocols with a large variation in the number of patients over differing periods of time. For this reason a formal meta-analysis has not been performed.

CONCLUSIONS

LN represents a spectrum of disease. 27% of LN cases diagnosed on CNB were found to contain malignancy on subsequent excision. Consequently, the evidence suggests that all patients diagnosed with LN on CNB should be considered for surgical excision; otherwise a diagnosis of DCIS or invasive carcinoma may be missed. There is no good evidence available to support the use of adjuvant therapies.

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Table-1: The incidence of breast cancer after excision biopsy for LN found on core biopsy.

Authors	Number of LN (LCIS/ALH) on CNB	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
Londero et al (2008)	21 LCIS	20	95	12(5 DCIS, 7 IC)	60
	14ALH	8	57	1 DCIS	13
El-Sayed et al (2003)	33 LN (unspecified)	33 LN (unspecified)	100	11 (6 DCIS, 5 IC)	33
O'Driscoll et al (2001)	7 LCIS	7 LCIS	100	3 (1 ILC, 2 DCIS)	43
Philpotts et al (2000)	5 LCIS	5 LCIS	100	1 DCIS	20
Burak et al (2000)	5 ALH	6ALH	100	1 DCIS	20
Berg et al (2004)	10 LCIS	8 LCIS	80	No carcinoma	0
	15 ALH	7 ALH	47	1 DCIS	14
Lechner et al (1999)	89 LCIS	58 LCIS	65	26 (10 IDC, 8 ILC, 8 DCIS)	45
	154 ALH	84 ALH	55	18 (3 IDC, 2 ILC, 13 DCIS)	21
Shin and Rosen (2002)	NA*	8 LCIS	14	3 (1 ILC, 1 DCIS, 1mixed)	25
	NA*	5 ALH	NA	No carcinoma	0
Middleton et al (2003)	35 LN (unspecified)	17 LN (unspecified)	49	6 IC	35
Houssami et al (2007)	23 LN (unspecified)	23 LN (unspecified)	100	14 (12 DCIS, 2IC)	61
Bauer et al (2003)	13 LN (unspecified)	7 LN (unspecified)	54	1 IDC	14
Crisi and Ricci (2005)	12 LCIS	21 LN	60	5 (3 IC – ipsi./ 2 IC contralateral)	15
	13 ALH				
	10				

Authors	Number of LN (LCIS/ALH) on CNB	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
	LCIS+ALH				
Georgian-Smith and Lawton (2001)	NA*	5 PLCIS	NA	2 ILC	40
Dmytrasz et al (2003)	13 ALH	7 ALH	54	3 (2 DCIS, 1 IDC)	43
Irfan and Brem (2002)	NA*	7 ALH	NA	1 DCIS	14
Dillon et al (2007)	12 LN (unspecified)	9 LN (unspecified)	75	4	44
Yeh et al (2003)	22 LN (unspecified)	15 LN (unspecified)	68	1 DCIS	7
Meloni et al (2002)	NA*	3 LCIS	NA	1 ILC	33
Pacelli et al (2001)	12 ALH	7 ALH	58	No carcinoma	0
	13 LCIS	7 LCIS	54	No carcinoma	0
	5 PLCIS	5 PLCIS	100	3 IC	60
Lieberman et al (2000)	16 LCIS	14 LCIS	88	3 (2 DCIS, 1 ILC)	22
	4 ALH	4	100	No carcinoma	0
Renshaw et al (2002)	36 LCIS	9 LCIS	25	No carcinoma	0
	35 ALH	6 ALH	17	No carcinoma	0
Arpino et al (2004)	45 LN	21 LN	47	3 (1 DCIS, 2 IC)	14
Elsheik and Silverman (2005)	25 ALH	20 ALH	80	5 (4 DCIS, 1 ILC)	25
	14 LCIS	13 LCIS	93	4 IC	37

Authors	Number of LN (LCIS/ALH) on CNB	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
Foster et al (2004)	15 LCIS	12 LCIS	80	4 (2 DCIS, 1 ILC, 1 IDC)	33
	20 ALH	14 ALH	70	2 DCIS	14
Mahoney et al (2006)	10 LCIS	20 LN (unspecified)	74	5 (2 DCIS, 3 ILC)	25
	15 ALH				
	2 PLCIS	2 PLCIS		1 IC	
Zhang et al (Jacob et al 2000)	10 LCIS	10		3 IC	30
	8 ALH	8		0	0
Lavoue' et al (2007)	70 LN (unspecified)	42 LN (classic)	74	10 (3 DCIS, 3 ILC, 1 IDC, 3 ILC)	19
		10 PLCIS			
Lee et al (2003)	18 LN (unspecified)	13 LN (unspecified)	72	6 (2 DCIS, 4 IC)	46
Menon et al (2008)	44 LN (unspecified)	25 LN (unspecified)	57	9 (1 DCIS, 7 IC, 1 PLCIS)	36
Brem et al (2008)	278 LN (unspecified)	67 LCIS	59	17 (7 DCIS, 6 ILC, 2 IDC, 2 unspecified IC)	25
		97 ALH		21 (15 DCIS, 3 ILC, 3 IDC)	22
Total	1229 LN	789 LN	64%	211 DCIS or IC	27%

LN: Lobular neoplasia. ILC: invasive lobular carcinoma. IDC: invasive ductal carcinoma. DCIS: ductal carcinoma in situ. IC: invasive carcinoma. The asterisk sign (*) in the table indicates these studies have reported only those cases of LN diagnosed both on CNB & subsequent surgical excision. Thus these numbers have been added to the total number of LN cases.

Table-2: The incidence of breast cancer after excision biopsy for LCIS found on core biopsy.

Authors	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
Londero et al (2008)	20	95	12 (5 DCIS, 7 IC)	60
Brem et al (2008)	67 LCIS	59	17 (7 DCIS, 6 ILC, 2 IDC, 2 unspecified IC)	25
Philpotts et al (2000)	5 LCIS	100	1 DCIS	20
Elsheik and Silverman (2005)	13 LCIS	93	4 IC	37
Foster et al (2004)	12 LCIS	80	4 (2 DCIS, 1 ILC, 1 IDC)	33
Berg et al (2004)	8 LCIS	80	No carcinoma	0
Meloni et al (2002)	3 LCIS	NA	1 ILC	33
Shin and Rosen (2002)	8 LCIS	14	3 (1 ILC, 1 DCIS, 1 Mixed)	25
Renshaw et al (2002)	9 LCIS	25	No carcinoma	0
O'Driscoll et al (2001)	7 LCIS	100	3 (1 ILC, 2 DCIS)	43
Pacelli et al (2001)	7 LCIS	54	No carcinoma	0
Zhang et al (Jacob et al 2000)	10	NA	3 IC	30
Liberman et al	14 LCIS	88	3 (2 DCIS, 1 ILC)	21

Authors	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
(2000)				
Lechner et al (1999)	58 LCIS	65	26 (10 IDC, 8 ILC, 8 DCIS)	45
Total	241 LCIS	61%	77 DCIS or IC	32%

Table-3: The incidence of breast cancer after excision biopsy for ALH found on core biopsy.

Authors	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
Londero et al (2008)	8 ALH	57	1 DCIS	12.5
Brem et al (2008)	97 ALH	59	21 (15 DCIS, 3 ILC, 3 IDC)	22
Elsheik and Silverman (2005)	20 ALH	80	5 (4 DCIS, 1 ILC)	25
Berg et al (2004)	7 ALH	47	1 DCIS	14
Foster et al (2004)	14 ALH	70	2 DCIS	14
Dmytrasz et al (2003)	7 ALH	54	3 (2 DCIS, 1 IDC)	43
Shin and Rosen (2002)	5 ALH	NA	No carcinoma	0
Renshaw et al (2002)	6 ALH	17	No carcinoma	0
Irfan and Brem (2002)	7 ALH	NA	1 DCIS	14
Pacelli et al (2001)	7 ALH	58	No carcinoma	0
Zhang et al (Jacob et al 2000)	8 ALH	NA	0	0
Liberman et al (2000)	4 ALH	100	No carcinoma	0
Burak et al (2000)	6ALH	100	1 DCIS	20
Lechner et al (1999)	84 ALH	55	18 (3 IDC, 2 ILC, 13)	21

Authors	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
			DCIS)	
Total	280 ALH	50%	53 DCIS or IC	19%

Table-4: The incidence of breast cancer after excision biopsy for Unspecified LN found on core biopsy.

Authors	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
Menon et al (2008)	25 LN	57	9 (1 DCIS, 7 IC, 1 PLCIS)	36%
Houssami et al (2007)	23 LN	100	14 (12 DCIS, 2IC)	61
Lavoue' et al (2007)	42 LN	74	7 (3 DCIS, 3 ILC, 1 IDC)	19
Dillon et al (2007)	9 LN	75	4 (unspecified)	44%
Mahoney et al (2006)	20 LN	74	5 (2 DCIS, 3 ILC)	25
Crisi and Ricci (2005)	21 LN	60	5 IC	15
Arpino et al (2004)	21 LN	47	3 (1 DCIS, 2 IC)	14
Yeh et al (2003)	15 LN	68	1 DCIS	7
Bauer et al (2003)	7 LN	54	1 IDC	14
El-Sayed et al (2003)	33 LN	100	11 (6 DCIS, 5 IC)	33%
Middleton et al (2003)	17 LN	49	6 IC	35
Lee et al (2003)	13 LN	72	6 (2 DCIS, 4 IC)	46%
Total	246 LN	69%	72 DCIS or IC	29%

Table-5: The incidence of breast cancer after excision biopsy for Pleomorphic LCIS found on core biopsy.

Authors	Diagnosis on CNB (cases with surgical biopsy)	Excision Surgery after CNB diagnosis of PLCIS (%)	Cancer on surgical biopsy	Cancer at surgical biopsy (%)
Georgian-Smith and Lawton (2001)	5 PLCIS	100	2 ILC	40
Pacelli et al (2001)	5 PLCIS	100	3 IC	60
Mahoney et al (2006)	2 PLCIS	100	1 ILC	50
Lavoue' et al (2007)	10 PLCIS	100	3 ILC	30
Total	22 PLCIS	100%	9	41%

Table-6: Summary of all studies of surgical excision biopsies for LN diagnosed on core biopsy, showing the incidence of cancer on final histology.

Total number of lobular neoplasia (LN), diagnosed on CNB	Total cases of surgical excision (%)	Histologic subtypes of LN on surgical excision	%age of subtypes on surgical excision	Total number of cancer identified on surgical excision (%)	Cancer subtypes (on histology) after surgical excision		PPV i.e. after surgical excision for cancer (%)
					Number of Invasive carcinoma (IC) (%)	Number of DCIS (%)	
					n=111 (53)	n=100 (47)	
n = 1229	n = 789 (64)	ALH (n= 280)	35	n=211 (27)	13 (5)	40 (14)	53 (19)
		LCIS (n = 241)	31		49 (20)	28 (12)	77 (32)
		Unspecified LN (n = 246)	31		42 (17)	30 (12)	72 (29)
		PLCIS (n= 22)	3		7 (32)	2 (9)	9 (41)

Figure 1

Lobular carcinoma in situ with complete filling and distortion of the lobular units by tumour cells
Inset: High power view of the lobular cells

