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Lobular Carcinoma *In Situ* (LCIS): Pathology and Treatment

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Abstract Lobular carcinoma *in situ* (LCIS) is not only a relative newcomer among breast lesions, but in its short span of 50 years it has gradually evolved from a rare form of breast cancer to being merely a marker of increased risk. This change has not been without controversy which persists to the present day, although there is now general agreement on the natural history of the disease.

The present report represents an update on current thinking about LCIS as well as a review of the limited number of studies dealing with the natural history of the lesion when treated by biopsy alone. Invasive cancer will develop in approximately 20–25% of women with LCIS provided there is sufficient follow-up after biopsy. Precise estimates are not possible since LCIS is an asymptomatic lesion that never makes a mass or reveals itself on mammography. It is found only by biopsy and thus the population being followed is a selected one. Every study has shown that when invasive cancer develops, it is just as likely to appear in the contralateral as in the biopsied breast, and invasive ductal cancers are more common than lobular. Clearly, the small round cells with pale cytoplasm that characterize LCIS do not go on to invasion in the usual patient; rather they serve to identify women who are more likely to develop breast cancer. Such patients represent a clearly defined group at increased risk, and for that reason are ideal candidates for chemoprevention. If tamoxifen or some other agent proves to be effective, the remaining arguments favoring mastectomy for LCIS will finally disappear.

Key words: Lobular carcinoma *in situ*

The juxtaposition of *in situ* and infiltrating carcinoma has always been somewhat contradictory since the diagnosis of carcinoma implies cells no longer confined by their normal boundaries. Broders, who refined the *in situ* concept in the 1930s, was aware of the problem but felt that progression from the *in situ* to the invasive stage of the disease was inevitable. In fact, proliferative lesions of the breast, with or without atypia, were designated as *in situ* cancers when the pathologist felt certain that invasive disease would follow. This reflected the fact that the two *in situ* lesions were seen in association with invasive cancers. Since the vast majority of breast cancers fall into the ductal category, the associated proliferative changes in ducts adjacent to the invasive focus were soon categorized as ductal carcinoma *in situ* (DCIS).

Lobular carcinoma *in situ* (LCIS) was identified in similar fashion when first reported by Foote and Stewart [1] in their 1941 report in the *American Journal of Pathology* based on 300 mastectomy specimens. They identified two patients with non-infiltrating lesions that had a distinctive histologic appearance. In the same series of patients they found 12 additional cases in which the lobular proliferation was accompanied by conventional invasive carcinoma, but with lobular histology. Foote and Stewart regarded both the *in situ* lobular lesion occurring alone and the lesion associat-

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ed with infiltrating lobular carcinoma as a single, special type of breast cancer. Their concept that both forms of lobular proliferation constituted a single malignant disease was generally accepted because it was consistent with the prevailing thought that *in situ* disease in the breast would inevitably progress to invasive cancer.

Haagensen, working in the Surgical Pathology Laboratory at Columbia Presbyterian Medical Center, was the first to question the inevitability of this progression. He found the *in situ* lesion in a number of benign breast biopsies and noted that the patients did well without further treatment. He was sufficiently convinced of the benign nature of lobular carcinoma *in situ* to change the name to lobular neoplasia. In this way he hoped to stop routine amputation of the breast by surgeons who were reacting to the word carcinoma. Years of controversy, primarily between physicians trained at Memorial Hospital and those at Columbia Presbyterian Medical Center, followed the publication of Dr. Haagensen's findings, and while he lost the battle (lobular neoplasia never replaced LCIS), he seems to have won the war (no more mastectomies).

HISTOLOGY

Mammary acini contain epithelial and myoepithelial cells. The rounded epithelial cells line the open central space, which creates the gland-like appearance characteristic of breast lobules. Beneath these cells are the myoepithelial cells that form a basement membrane. The cells that proliferate in LCIS evolve from the epithelial component and fill the lumen, forming solid rounded units. These new neoplastic cells are slightly larger than normal acinar cells and their cytoplasm is paler. As the cells multiply, they fill and distend the acinar structures that make up the breast lobule. Because the cells are round and rather uniform, the picture suggests a bag of marbles. The histologic appearance is distinctive and can be differentiated readily from that of other proliferative lesions of the breast. Unfortunately, borderline lesions exist related not so much to appearance as to minimal changes, such as only a fraction of the acini in a lobule [2].

The ducts may also be affected by extension from the lobules, but the distinctive cells are still involved. While DCIS may involve the lobules, it does not pose a problem for experienced pathologists. However, there are instances where both *in situ* lesions will co-exist in the same breast.

INCIDENCE

The true incidence of LCIS is not known, as the lesion does not form a palpable tumor and therefore cannot be identified clinically. Inability to detect the lesion other than with a microscope carries over to mammography. At one time it was thought that LCIS was associated with calcium deposition [3,4], but this simply reflects the fact that microcalcifications are a common cause for mammographically triggered breast biopsies. When LCIS is biopsied in such a patient, the microcalcifications are not in the involved acini. Just as is the case in biopsies for palpable lesions, the lump has nothing to do with LCIS; the LCIS is found by chance simply because involved breast tissue was sampled and examined histologically. A recent radiology review again confirmed the lack of mammographic findings specific for LCIS [5].

Biopsy material serves as our largest source of information concerning the incidence of LCIS, but these patients constitute a selected population. Since the biopsy was done for something other than LCIS, the frequency will depend on the amount of tissue excised and especially the care with which it is examined. Even a biopsy examined on multiple slides represents only a small fraction of the total breast epithelium.

Despite these limitations, breast biopsies provide valuable information concerning the incidence of LCIS, and a number of extensive reviews have been carried out. Haagensen reviewed more than 5000 patients who underwent biopsy between 1930 and 1972, and identified 211 cases of LCIS. This constituted 3.6% of all benign epithelial breast lesions [6]. A slightly lower figure was reported by Wheeler [7], who reviewed 3570 benign biopsies and reported an incidence of 0.8%; whereas Andersen [8] found LCIS in 1.5% of 3299 specimens.

Autopsy studies of women dying without breast disease avoid some of the problems associated with biopsy material, but histologic examination of all breast tissue represents an enormous effort, and has been rarely accomplished. Furthermore, LCIS may regress after menopause or once estrogen stimulation of the breast has ceased to be a factor, and autopsy data reflect an older

population. There is no question that every LCIS series shows a marked preponderance of premenopausal patients, but it is not entirely clear if this reflects regression or the fact that the overwhelming number of benign epithelial lesions that result in breast biopsies appear during the reproductive years. It will be interesting to see if the recent widespread use of post-menopausal estrogen replacement will alter the LCIS age distribution.

Clearly biopsy and autopsy data reflect different populations, but the incidence of LCIS in both groups is extremely low. One of the most extensive autopsy studies was carried out at Columbia by Frantz and associates [9], and while the subject was cystic disease, Dr. Frantz was well aware of Dr. Haagensen's interest in LCIS. The median age in the 225 autopsies was only 45 years, but no LCIS lesions were noted.

In another autopsy series, an appreciable number of *in situ* lesions were found [10]. This Danish study has been criticized because of its overly broad definition of both DCIS and LCIS, but the authors felt that the high incidence reflected meticulous examination (57–166 blocks per breast) in a population with a high breast cancer incidence. However, Alpers and Wellings [11] failed to confirm these findings despite equally painstaking histologic examination. They reported no instances of LCIS in 101 patients; this was also true in a similar study by Kramer and Rush [12]. The presence of breast cancer, or death from breast cancer, in the autopsied patients increases the incidence of LCIS.

Although neither biopsies nor autopsies provide the true LCIS incidence, these studies allow certain conclusions. First, LCIS is a rare lesion in the general population because even the selection associated with biopsy material yields only a 2–3% incidence. Autopsy studies suggest that the true incidence is even lower (<1%) but rises when breast cancer patients are involved, suggesting an association with invasive cancer.

NATURAL HISTORY

Haagensen and other breast pathologists convincingly established that the majority of patients with LCIS treated by biopsy alone will not develop invasive cancer despite long periods of follow-up [6–8,13]. These large retrospective studies were primarily reported in the 1970s. Little has been done since, given the time commitment involved in reviewing thousands of benign breast biopsies. This may actually be easier than doing follow-up studies designed to trace women who may well change their names, to say nothing of their locations, over the next 10–20 years.

The largest retrospective review was reported by Haagensen, who amassed 297 patients with LCIS biopsied between 1930 and 1977 [6]. All but 4 patients were observed for a minimum of 5 years, and 208 of them from 11 to 47 years. Only 2 patients were lost. Carcinoma developed in 63 patients (21%). In 10 patients, LCIS was noted in the remaining breast following mastectomy. If these women are excluded, as is the case in all other series, the percentage falls to 18%. The other large series comes from Memorial Hospital in New York; when last updated by Rosen, there were 99 patients [13]. The follow-up was even longer and 37% developed invasive cancer. However, the long interval between the original biopsy and the review made it difficult to trace some of the patients, resulting in a lost-to-follow figure of 16%. Smaller series published by Wheeler [7] and Andersen [8] reported that 17% and 29% of the patients, respectively, developed cancer.

The percentage of patients developing invasive cancer may not be the best way to assess LCIS risk because it depends on length of follow-up and the number of lost patients. The ratio of observed-to-expected cases is preferable as a means of expressing risk, since it not only takes into account the years of follow-up, but also the age of the patient, an important risk factor. Haagensen and Rosen both utilized data from the Connecticut Tumor Registry for the baseline rate, and reported ratios of 6.9 to 1 and 9 to 1, respectively. Therefore, the risk as calculated from the two largest series is similar and provides a reliable estimate of the risk faced by LCIS patients.

The risk of invasive cancer affects both the biopsied and the contralateral breast equally. Despite this, it has not been possible to routinely demonstrate the lesion in the contralateral breast. Tissue was available from both breasts in 73 of Haagensen's patients, but only 19 (26%) had bilateral LCIS. It is not clear if this reflects spotty distribution of the lesion or limited material, since most of the contralateral tissue came from biopsies.

Mirror image or blind, upper outer quadrant

biopsies provide similar information [14,15]. It is worth noting that the highest rates of bilaterality are reported in studies in which either total or subcutaneous mastectomy served to obtain the tissue, suggesting that distribution of LCIS in the breast is not uniform and the chance of finding the lesion is related to the quantity of tissue available for study.

TREATMENT

Treatment of LCIS has changed along with the change in thinking about its natural history. It would be naive not to mention that more recent efforts to conserve the breast have also played a role in this change. Originally there was no debate since the prevailing opinion stated that LCIS was the *in situ* form of invasive lobular cancer and progression to invasive disease was inevitable. Once it became clear that the majority of patients with LCIS did not go on to develop invasive cancer, treatment was no longer straightforward.

The small round cells with pale cytoplasm that fill and distend the acini are not the enemy. The best evidence to support this view comes from patients with LCIS who go on to develop invasive cancer. The most common histologic type is infiltrating ductal carcinoma; the lobular carcinoma cells are not part of the picture. For this reason re-excision of biopsy sites and the concept of clear margins are not relevant. The thought that LCIS risk might be excised makes no more sense than trying to excise a positive family history. The cells in and of themselves are not the danger; rather, the presence of LCIS serves as a marker of increased risk. Since the risk is bilateral, rational treatment requires equal attention to both breasts.

Efforts have been made to identify the fraction of LCIS patients who go on to invasive cancer. Unfortunately, such efforts have been limited to histologic studies such as grading the severity of the LCIS and attempting to correlate such findings with the development of breast cancer. Haagensen was not able to show any relationship, but he was able to show that risk factors are cumulative. The combination of a positive family history for breast cancer and LCIS raised the observed-to-expected ratio to more than 10, and may well be a factor in treatment recommendations.

There would be little debate about treatment if a truly effective method of surveillance was available. Haagensen initiated his policy of observation coupled with close follow-up. Patients were seen every 4 months and had annual mammograms in the expectation that if cancer developed, it would be detected early enough to institute successful treatment.

Current thinking about breast cancer biology casts doubt on these more optimistic concepts; both doctors and patients are asking whether early is early enough. The recently reported Canadian National Screening study [16] has once again questioned the ability of mammography to reduce breast cancer mortality in women under 50 years of age, the age group usually affected by LCIS. Haagensen always pointed out that most of the breast cancer deaths in his LCIS series occurred in women who failed to return for follow-up, but current evidence suggests that even the most vigorous monitoring cannot routinely diagnose cancer in a curable stage.

Therefore, the key issue relates to the severity of the risk facing patients with LCIS. Although it may not be cancer, the observed-to-expected ratio of developing invasive cancer indicates that patients with LCIS are facing difficult choices: (1) observation, recognizing its limitations; (2) ipsilateral mastectomy with contralateral biopsy, the fate of the other breast being determined by the biopsy result; and (3) bilateral mastectomy. Some would add subcutaneous mastectomy to the list, but if it is to be cosmetically acceptable, it will leave breast tissue behind, nullifying the sense of security that resection is expected to provide.

Radiation therapy has been applied sporadically, but there has been no systematic study of this approach. It makes little sense to think that one can radiate away risk, but radiation plus tamoxifen is being tested as a possible treatment for DCIS. Tamoxifen alone is also being investigated, but its ability to ward off invasive cancer is uncertain at this time.

A great deal has changed since Drs. Haagensen of Columbia Presbyterian Medical Center and Urban of Memorial Hospital and their allies battled over the proper treatment of LCIS. Urban advocated mastectomy on the involved side with contralateral biopsy [14]. As noted above, contralateral biopsy would be expected to show lobular carcinoma *in situ* in approximately 25% of the

patients, but the remaining 75% whose biopsies were negative would still be exposed to the same risk as those women being treated by mastectomy on the same side as the original biopsy [17].

Urban's approach was based on the original Memorial Hospital view of LCIS as a premalignant lesion, which was clearly illogical once Haagensen established LCIS to be a bilateral marker of increased risk, rather than cancer. However, the Haagensonian approach of observation was also flawed because he felt the increased risk of invasive cancer could largely be ameliorated by early detection. Our thinking about early detection has also undergone change, while at the same time microvascular surgery has opened up new and dramatically improved approaches to breast reconstruction.

Now that LCIS is accepted as a marker for invasive cancer without direct participation in the process of malignant transformation, unilateral mastectomy is no longer a rational treatment. A recent questionnaire sent to surgical oncologists suggests that observation is the treatment recommended by the majority of American physicians. However, bilateral total mastectomy has assumed a slightly larger role for a number of reasons. First of all, the introduction of lumpectomy for invasive breast cancer did not do away with mastectomies, despite its major impact. Secondly, both physicians, and more significantly, women, have come to appreciate the limitations of surveillance designed to insure early detection. Finally, plastic surgeons have properly abandoned subcutaneous mastectomy for LCIS and turned to innovative new reconstruction techniques that make total mastectomy less devastating.

SUMMARY

Lobular carcinoma *in situ* is a relatively new breast lesion, first described only 50 years ago. It was originally thought to be a step in the progression to invasive lobular cancer, but current evidence suggests that it is a marker of increased risk. It is certainly the most powerful of all risk factors, with studies suggesting that 20–30% of patients will go on to develop invasive cancers of varying histologic types, and occurring with equal frequency in the biopsied and opposite breasts. In that sense, LCIS patients would be ideal candidates for chemoprevention. However, long periods of follow-up would be needed unless surrogate endpoints can be established. At this time, diagnosis is based entirely on histology, and evidence suggests random distribution of the lesion in the breast. Repeated blind cytology aspirates or core biopsies can be performed without morbidity, but ways to detect associated histologic or cytologic features with a more uniform distribution in the breast would have to be developed. Identifying LCIS patients who will develop invasive cancer has eluded pathologists to date. New imaging techniques may be more fruitful, but mammography and ultrasound have not been effective. Instruments that attempt to quantitate depolarization across cancerous epithelium constitute a new approach that might record reversible abnormalities in LCIS patients. Finally, the wide variety of molecular techniques being applied to invasive neoplasms and DCIS, which might serve as surrogate endpoints, have yet to be employed in LCIS patients. The arrival of chemoprevention protocols has heightened interest in LCIS. Because of increased risk, and the fact that observation is the accepted treatment, such patients are strong candidates for chemoprevention trials. A better understanding of the evolution of the lesion over time and the mechanisms involved in carcinogenesis is needed.

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