The Clinical Management of a Normal Contralateral Breast in Patients with Lobular Breast Cancer

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Ninety-nine patients with the diagnosis of lobular carcinoma (LC) treated between 1970 and 1981 were reviewed. Thirteen patients had a contralateral mastectomy for duct cancer (DC) before the diagnosis of LC. Ten of the remaining 86 patients (11%) had simultaneous bilateral cancers detected by either physical examination or mammography, none by blind biopsy. Three of the surviving 38 patients (7.8%) developed a contralateral cancer an average of 143 months after operation. In comparison 167 patients with DC treated during the same period of time had a 1.8% incidence of synchronous cancer but the same incidence of subsequent cancer (7%). Lobular carcinoma *in situ* was not a reliable marker for predicting the presence of cancers in the contralateral breast. The diagnosis of LC is not an indication for either biopsy or removal of a normal contralateral breast.

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THE CLINICAL MANAGEMENT OF patients with invasive lobular carcinoma of the breast is controversial. Some authors advise routine biopsy of a normal contralateral breast, while others advocate a prophylactic contralateral mastectomy. In contrast Fisher[1] advocates nothing more than routine follow-up of the contralateral breast of the patient with invasive lobular carcinoma. This study was designed to determine the long-term clinical course of patients with invasive lobular carcinoma of the breast and thus further define indications for biopsy or excision of a contralateral breast that is normal on physical examination and mammography.

Clinical Material

The surgical pathology files between 1971 and 1980 were reviewed for all patients with diagnosis of either pure lobular carcinoma (LC) or lobular carcinoma with duct features (LC/DC). On review of the histologic sections of the primary tumor, a diagnosis of LC (69 cases) or LC/DC (30 cases) was confirmed in 99 patients. The histologic sections of these 99 patients were also reviewed to determine the incidence of lobular carcinoma *in situ* (LCIS) in association with a diagnosis of LC or LC/DC. As a control group, 167 patients who survived for 120 months with infiltrating duct cancer (DC) were randomly pulled from the Tumor Registry files between 1970 and 1975. The histologic sections were reviewed to confirm the diagnosis and these patients were followed for an average of 144 months.

At the time of the diagnosis of lobular carcinoma, the 99 patients ranged in age from 30 to 70 years (average age, 54 years). Before treatment the contralateral breast was examined by physical examination and the majority of patients had a mammogram. All patients had a chest x-ray and a serum alkaline phosphatase determination. Scintiscans of the liver and bone were not performed on a routine basis. Two patients with synchronous cancers had either radiographic or scintiscan evidence of systemic metastasis on initial evaluation. None of the remaining 97 patients had clinical or radiographic evidence of systemic metastasis. With the exception of the two patients with systemic metastasis, all patients were treated by modified radical mastectomy or radical mastectomy.

Results

The incidence of synchronous or asynchronous invasive carcinomas in the contralateral breast of these patients is reviewed in Table 1. There was no statistically significant difference between the incidence of bilaterality in patients

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TABLE 1. *Invasive Lobular Carcinoma and Invasive Lobular/Duct Carcinoma Incidence of Bilaterality*

Lobular Carcinoma (n = 69)	
20/69 (28%) with bilateral disease*	
10 previous	(10 DC)
7 simultaneous	(6 DC, 1 LC)
3 subsequent	(2 DC, 1 LC)
Lobular/Duct Carcinoma (n = 30)	
6/30 (20%) with bilateral disease*	
3 previous	(3 DC)
3 simultaneous	(1 DC, 2 LC)

* There was no statistically significant difference in the incidence of bilaterality between invasive lobular and invasive lobular/duct carcinoma.
DC, infiltrating duct cancer; LC, infiltrating lobular cancer.

with LC compared to LC/DC ($p < 0.4$).* In view of these similar clinical courses, the two groups were combined for further analysis.

Thirteen of the 99 patients had a contralateral mastectomy for DC 10 to 168 months (average 74) before the diagnosis of LC. Eight of these patients survived for an average of 88 months without evidence of recurrence after treatment for LC in the ipsilateral breast. Four patients died of metastatic breast carcinoma 24 to 144 months after operation and one died of unrelated causes.

Ten of the remaining 86 patients had simultaneous carcinomas in the contralateral breast (seven DC, three LC). Six of the simultaneous contralateral carcinomas were detected by physical examination, four by mammography alone. Two of these patients had radiographic or scintiscan evidence of metastasis on initial clinical assessment and died 41 and 70 months after initial clinical assessment. Seven of the remaining nine patients died an average of 66 months after operation, and one remains alive 89 months after operation.

Thirty-eight of the remaining 76 patients who survived the initial tumor were followed for 70 to 174 months (average 106 months). Three patients developed a subsequent carcinoma in the contralateral breast 113, 156, and 161 months after treatment of the initial lobular carcinoma (one DC, two LC). One patient has survived for 37 months without evidence of metastasis, and the other two patients died 10 and 36 months after operation of systemic metastasis.

Of the 99 cases reviewed, 61 (61%) had evidence of LCIS in the ipsilateral breast. The influence of LCIS on the incidence of bilaterality is reviewed in Table 2. There was no correlation between the incidence of LCIS in the ipsilateral breast and the incidence of synchronous or asynchronous invasive carcinomas in the contralateral breast ($p < 0.17$).

* Statistical evaluations were done by Fisher Exact Test.

TABLE 2. *Influence of Lobular Carcinoma* in Situ *on Bilaterality*

Total number of cases with LCIS	61 (61%)
Total number of cases without LCIS	38 (38%)
Incidence of bilateral disease in cases with LCIS	14/61 (22%)
Incidence of bilateral disease in cases without LCIS	12/38 (31%)

LCIS, Lobular carcinoma *in situ.*
These differences were not statistically significant.

The clinical course of 167 patients with DC as compared to that of patients with LC is reviewed in Table 3. The incidence of simultaneous primary carcinomas was significantly increased in those patients with LC. The incidence of subsequent carcinomas in the contralateral breast was essentially equal in patients with LC compared to those with DC.

Discussion

Invasive lobular cancer is not a common tumor. Fisher[2] reports an 8.2% incidence of LC or LC/DC in a series of 1000 cases of invasive breast carcinoma. In Fisher's experience[2] these tumors were not multifocal in origin, all of the lobular carcinomas were confined to the quadrant containing the palpable mass, and there was no evidence of microscopic tumor in quadrants remote from the quadrant of origin. In spite of these histologic observations, there is a 25% clinical incidence of either synchronous or asynchronous carcinomas in the contralateral breast of patients with LC and an even higher incidence of LCIS. The relationship between LCIS and LC remains somewhat obscure. The two lesions are frequently seen together but a number of studies have demonstrated that LC can be present alone. The clinical behavior of LC *versus* LCIS is also considerably different. LC is a malignant tumor with the same potential for metastasis as DC

TABLE 3. *Bilaterality and Invasive Carcinoma*

Contralateral Breast	Lobular Cancer (n = 99)	Infiltrating Duct Cancer (n = 167)	p value
Simultaneous primaries	10/99 (10%)	2/167 (1.2%)	< 0.0003
Subsequent primaries	3/38 (7.8%)	14/165 (8.3%)	< 0.04
Previous infiltrating duct carcinoma	13/99 (13%)	NA	
Total	26/99 (26%)	16/167 (9.5%)	< 0.0001

NA, not applicable.

TABLE 4. *A Comparison of Results of Ashikari's Study with Current Study—Lobular Carcinoma*

Contralateral Breast	Ashikari's	Current Study
Contralateral cancers	79*/349: 23%	26/99: 26%
Previous	21 (26%)	13 (50%)
Simultaneous	28 (35%)	10 (38%)
Subsequent	30 (38%)	3 (12%)

* 25% LCIS.

in contrast to LCIS, which is a premalignant lesion. Patients with histologic evidence of LCIS alone have a 25% chance of developing either a DC or LC in either breast within the next 25 years. We would agree with Fisher[1] that a number of clinical series discussing the bilaterality of LC have included a significant number of patients in whom the tumor in the contralateral breast has been LCIS.

Because LC is a relatively uncommon lesion there are not a large number of clinical cases reported in the literature. Ashikari[3] reports the largest series of patients with LC, 349 patients with a 23% incidence of either synchronous or asynchronous carcinoma in the contralateral breast. Although 25% of these patients had only LCIS in the contralateral breast, the overall results were similar to the current study (Table 4). We must then address the issue as to how this 25% incidence of bilateral disease should affect the clinical management of a normal contralateral breast in patients with LC.

As previously noted any discussion of the clinical management of LC is complicated by the relatively small number of cases in any one series and the tendency of some authors to refer to LCIS as if it were an invasive lesion. Some authors advise biopsy of the contralateral breast in patients with LC. Donegan[4] describes a group of 36 patients with LC and/or LCIS. Although none of the patients with LC had a simultaneous biopsy of a normal contralateral breast, the authors advise biopsy of a normal contralateral breast in patients with LC. In evaluating the use of a contralateral biopsy in a large number of patients with invasive breast carcinoma, Anderson[5] describes a 50% incidence of a positive biopsy in six patients with LC. However all the contralateral biopsies revealed LCIS rather than invasive carcinoma. Wilson and Alberty[6] report that each of their five patients with lobular carcinoma developed a contralateral carcinoma and therefore advocate biopsy of the contralateral breast. Newman[7] advocates a biopsy of the contralateral breast on the basis of his experience with 67 patients with LC, 10% of whom developed a contralateral invasive carcinoma within 13 to 80 months of the initial lesion.

Benfield[8] and Warner[9] advocate a prophylactic contralateral mastectomy in patients with LC, both authors basing their conclusions on the same group of patients. Although they describe a 70% incidence of multicentricity and a 59% incidence of bilaterality in patients with LC, their statistics appear to be based predominantly on patients with LCIS. Only seven patients with LC are described in either publication. McCredie[10] also advocates a prophylactic contralateral mastectomy based on the fact that 2% of the patients in their experience with subsequent carcinoma in the contralateral breast had LC. Fechner[11] describes a group of 35 patients with LC, five of whom developed an invasive carcinoma in the contralateral breast. Two of these carcinomas occurred within 5 months of the diagnosis of LC in the ipsilateral breast, two within 35 months, and one 14 years later. On the basis of this experience, he advocates excision of a normal contralateral breast in patients with LC. Although Davis[12] does not specifically advocate a biopsy or contralateral mastectomy in patients with LC, he presents perhaps the most convincing data for such an approach. He describes 48 patients with LC, 19 of whom had "an operative evaluation of the opposite breast." Almost 50% of these 19 patients were found to have invasive cancer in the contralateral breast. The exact status of the opposite breast is not described, *i.e.*, its normalcy on physical examination and mammography.

Although our experience with LC is somewhat muted by a high incidence of previous DC, we would agree with Fisher[1] that there is no indication for routine biopsy or excision of a normal contralateral breast in patients with LC. Management of the contralateral breast will not be an issue if it has been previously removed for DC. The presence of LCIS in the ipsilateral breast did not prove to be a reliable indicator of either synchronous or asynchronous cancer in the contralateral breast and therefore could not be used as an indication for biopsy of a normal contralateral breast. None of the normal contralateral breasts in this series were biopsied. We have concluded that we did not miss occult invasive carcinomas in the contralateral breast because subsequent carcinomas, if they did occur, were detected at least 9 years later. This series confirms the fact that synchronous carcinomas are considerably more common in patients with LC compared to patients with DC. Although subsequent carcinomas did occur in the contralateral breast of patients with LC, their occurrence was remote and their incidence was similar to the number of subsequent carcinomas that occurred in patients with DC.

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Discussion

DR. CHARLES M. BALCH (Houston, Texas): I rise to support the basic conclusions that Dr. Baker has made. I would mention, however, that the incidence of invasive carcinoma in the opposite breast does increase as a function of time and follow-up. Some of those studies, both from Memorial Institute and our own, have shown that the incidence of invasive cancer continues to increase over time so that at 20 years it may be as much 15%; however it may still be relatively low at 4% to 5% after only 10 years of follow-up.

There is controversy about the management of the opposite breast because the number of patients is so small. We still do not know whether there are any risk factors that can portend a high probability of developing a second cancer in the opposite breast of a patient with lobular carcinoma of the breast.

One aspect of this problem that was analyzed at the M. D. Anderson Cancer Center involves the geometric location of opposite breast cancers. As you recall it was about 20 years ago when a routine biopsy of the opposite breast was advocated by many surgeons, and if a blind biopsy was done, it should be performed at the "mirror image" location. In fact, our analysis of opposite breast cancer showed that there was no geometric relationship whatsoever. The majority of second carcinomas were located in the upper outer quadrant or the central area. For example, an inner quadrant lesion on one side would not portend an inner quadrant lesion on the opposite side.

Furthermore we would make some distinction between a sparse amount of LCIS around the tumor or elsewhere in the breast and extensive LCIS and have used this as one criteria for biopsies of the opposite breast. This would be especially true in situations in which the opposite breast was difficult to follow because of underlying fibrocystic disease, the patient was unable to have regular follow-up exams, or there was significant and genuine cancer phobia.

The point I would like to make is that if one is going to perform opposite breast biopsies, they should be done sparingly and should not be directed to a mirror image location but in the upper outer quadrant of the opposite breast.

I had three questions I wanted to ask Dr. Baker. First are there any subsets of patients who are at higher risk for developing an opposite breast cancer in their study? Second did they find, as we did, any lack of geometric relationship between the opposite breast cancers? Finally if one is conservative in following these patients without biopsies or mastectomies, it presumes that the screening process would detect an opposite breast cancer at an early and highly curable stage. So my third questions is: In those patients who developed opposite breast cancer, what was the stage and survival of those patients who were followed?

DR. ROBERT P. HUMMEL (Cincinnati, OH): I just rise to make a few comments. The first is that I would certainly agree with Dr. Baker's bottom line that invasive carcinoma of the breast, be it lobular or ductal, seems to act the same. We have reviewed our cases at the Breast Consultation Center in Cincinnati and find that the incidence of bilaterality, lymph node metastases, and so on, is similar once the tumors are invasive.

One of my questions is an elaboration of Dr. Balch's question. It would seem that the recommendations in this paper are based on the ability to follow these patients closely for any recurrent tumor because the percentage of recurrence is high over a period of a number of years. We know there may be a number of difficulties in following patients, including lack of patient follow-up cooperation and the difficulty of evaluating the breast on physical exam. Other patients have difficult mammograms to read. Others have strong family histories of carcinoma of the breast or may show on their biopsy extensive wide-spread dysplasia in the breast specimen along with the original lobular carcinoma. So my question is: Are you influenced by these factors in your recommendations to the individual patient, or do you follow them all regardless of the circumstance?

The other question I would have is that it would seem to me there is even more controversy as to how to treat lobular carcinoma *in situ*, not only in the opposite breast but the same breast. Are you satisfied with a lumpectomy alone or do you recommend any further treatment? I wondered if, after going through these data and looking at your experience with lobular carcinoma both *in situ* and invasive, you have any recommendations about the *in situ* variety of the disease?

DR. FRANK E. GUMP (New York, New York): I would like to congratulate the authors for looking at this topic since it has fallen out of favor in the age of breast preservation.

The series at Columbia is very similar in the sense that we have about the same number of patients, and the only difference has to do with the way that we have looked at the relationship of lobular carcinoma *in situ* to the question of the opposite breast.

I think one of the major differences is the way in which we presented our data. Percentages are very dependent on length of follow-up. If you look at the observed-to-expected ratio, you cannot only deal with that problem, but you can also deal with other risk factors such as family history and patients' ages, which would be important considerations.

The patients who had pure lobular lesions in our series had a 3- to-1 observed-to-expected risk ratio, and this was no different than some 3000 patients who had ductal carcinoma. The difference, though, was in patients who had both the invasive lobular and the *in situ* lobular lesions; here the ratio was 8 to 1. In other words, there was a clear difference when this was added to the invasive lesion. In that sense, we would not agree that the presence of lobular carcinoma *in situ* does not influence the risk on the opposite side. However before closing these remarks, I should say that the same 8-to-1 ratio is true whether you add the lobular *in situ* lesion to an invasive lobular or a ductal lesion, so this is simply a reflection of this marker of increased risk, which is the way we have always looked at lobular carcinoma *in situ*. In fact Dr. Haagensen wanted us to call it lobular neoplasia.

DR. JOHN S. SPRATT (Louisville, Kentucky): I have just a comment and a question. In looking at asynchronous cancers, it is very important to look at the incidence per age-specific man years of observation. This has been shown by the classic work by Schoenfield on multiple primary cancers, and we used the same methodology at the cancer hospital in