

Noninvasive Breast Carcinoma

Frequency of Unsuspected Invasion and Implications for Treatment

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One hundred twenty-nine biopsies from 121 patients with a frozen or paraffin section diagnosis of noninvasive breast carcinoma were studied. Eight women had bilateral noninvasive carcinoma. Seven biopsies reported as intraductal on frozen section contained invasive carcinoma on paraffin section. Of the remaining 122 biopsies proven to have noninvasive carcinoma on paraffin section, 39 (34%) were reported at frozen section and as noninvasive carcinoma, 24 (20%) as atypical and 59 (48%) as benign. Intraductal carcinoma (IDC) was identified more often at frozen section (45%) than was lobular carcinoma in situ (19%). Among 41 patients who had bilateral carcinoma with invasive disease in one breast, 76% of contralateral noninvasive carcinoma was LCIS. After excisional biopsy, carcinoma was found in 56% of 103 mastectomy specimens, including invasive carcinoma in 6% of breasts with IDC and 4% with LCIS. Residual noninvasive carcinoma was usually of the same type found at biopsy (90% IDC and 88% LCIS) and involved quadrants other than the biopsy site in 33% with IDC and in 80% with LCIS. When the frozen or paraffin section diagnosis of a generous excisional biopsy was noninvasive breast carcinoma, there was a substantial risk that foci of the same type of noninvasive carcinoma were also present in other quadrants. However, occult foci of invasive carcinoma were quite infrequent and the risk of axillary metastases was very low. Adequate treatment for noninvasive carcinoma requires elimination of all residual foci of noninvasive disease. At present this can best be accomplished by total mastectomy if the operation is properly performed. To insure removal of the axillary extension of the breast and for staging, in continuity dissection of the lowest axillary lymph nodes is also prudent.

THE DIAGNOSIS AND TREATMENT of noninvasive mammary carcinoma are among the most complex clinical problems encountered in the management of

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breast disease. While the histological criteria for diagnosis are generally agreed upon, borderline situations exist that may be subject to differing interpretations.¹⁴ The lesions are rarely grossly apparent and especially in the case of lobular carcinoma in situ (LCIS) are often found unexpectedly. Thus, noninvasive carcinoma detected in paraffin sections is a frequent cause of a false negative frozen section report.¹⁵

Controversy exists regarding the treatment of noninvasive and minimally invasive breast carcinoma. Some have questioned the need for mastectomy to treat these lesions and recommend partial mastectomy, radiation therapy, or simply careful followup.^{1,8,9,10,23} Advocates of mastectomy with axillary dissection have emphasized the possibility that the breast might harbor occult invasive carcinoma and that this might be the source of unsuspected metastases.² However, there is little information available regarding the magnitude of these risks. To study this question we have undertaken a detailed study of a large group of patients with noninvasive carcinoma at biopsy.

Materials and Methods

The patients were identified for this study in the course of a multifaceted investigation of breast carcinoma that began in October, 1976. Data was obtained from pathology reports and from a review of histological sections in each case by one of the authors (PPR). A total of 1175 consecutively treated patients with primary operable breast carcinoma had been accessioned in the study by August 1978 when data collection relating to noninvasive carcinoma was completed.

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Results

Comparison of Frozen and Paraffin Section Diagnoses

All patients whose diagnosis recorded for either a frozen section or final paraffin section was noninvasive carcinoma were identified. One hundred twenty-nine biopsies obtained from 121 patients (eight had bilateral noninvasive carcinoma) were found. Not included were seven other patients whose biopsies revealed infiltrating carcinoma on paraffin section after the frozen section was interpreted as benign or atypical, since neither the frozen nor the paraffin section showed only noninvasive carcinoma. In the entire series of 1175 patients reviewed there were no cases in which a frozen section diagnosis of carcinoma was not confirmed by paraffin section.

Overall results. Details of the relationships between frozen and paraffin section diagnoses are present in Table 1. Forty-six biopsies were reported as noninvasive carcinoma at frozen section. Seven of the 46 biopsies reported as noninfiltrating on frozen section proved to contain invasive carcinoma on paraffin section. Thus, 122 biopsy specimens contained only noninvasive carcinoma after frozen and paraffin section evaluation, and of these, 39 or 34% had been identified as such in the frozen section. The diagnosis was deferred to paraffin section for 24 other biopsies (20%) because atypical or borderline changes were noted at frozen section. Noninvasive carcinoma was unanticipated in 59 or 48% of the total group.

Intraductal carcinoma. Among patients proven to have only intraductal carcinoma (IDC) on the paraffin section, 27 or 45% were identified at frozen section. Atypia had been noted in another 17%. The diagnosis of carcinoma was unanticipated in 23 or 37% of patients with intraductal carcinoma.

TABLE 1. Relationships Between Frozen Section and Final Paraffin Section Diagnosis in 129 Biopsies from 121 Patients

Paraffin Section Diagnosis (Total Biopsies)	Frozen Section Diagnosis (Number Biopsies)				
	IDC	LCIS	ADH	ALH	Benign
IDC (60)	27		9	1	23
IFDC (7)	7				
IDC & LCIS (3)	1		1	1	
LCIS (59)		11	2	10	36
Total 129	35	11	12	12	59

* Eight patients had bilateral non-invasive carcinoma on paraffin section. In 5 cases both biopsies were interpreted as benign or atypical at frozen section. In two others, one frozen section was reported as carcinoma and the other as benign or atypical. The eighth patient had bilateral intraductal carcinoma on frozen and paraffin section.

IDC: intraductal. ADH: atypical duct hyperplasia. IFDC: infiltrating lobular. LCIS: lobular *in situ*. IFDC: infiltrating lobular. ALH: atypical lobular hyperplasia.

TABLE 2. Relationship Between Paraffin and Frozen Section Diagnoses of Contralateral Breast for 41 Patients with Invasive Carcinoma of One Breast*

Paraffin Section Diagnosis (Total Biopsies)	Frozen Section Diagnosis (Number Biopsies)				
	IDC	LCIS	ADH	ALH	Benign
IDC (9)	1		1		7
IDC & LCIS (1)				1	
LCIS (31)		3	3	7	18

* For explanation of abbreviations, see Table 1.

Lobular carcinoma in situ. Eleven or 19% of 58 biopsies that ultimately revealed LCIS were interpreted as such at frozen section. In 12 (20%) other cases the diagnosis had been deferred when atypia was reported in the frozen section. The frozen section was reported as benign* in 36 or 61% of biopsies ultimately proven to contain LCIS.

Intraductal carcinoma and lobular carcinoma in situ. Three patients were found to have IDC and LCIS on paraffin section. One of these biopsies had been reported as IDC at frozen section and in 2 atypical hyperplasia has been noted.

Discrepancies in Frozen-Paraffin Diagnoses and Bilaterality

Bilateral carcinoma was found in 49 or 40% of the 121 patients. In 41 cases the contralateral lesion was clinically apparent infiltrating carcinoma or there had been a prior contralateral mastectomy. Eight other women who had simultaneous bilateral noninvasive carcinoma are described in detail in the legend to Table 1.

Table 2 shows the correlation between frozen and paraffin section diagnoses for biopsies of the contralateral breast in women with concurrent or prior clinically apparent infiltrating carcinoma. Carcinoma was reported at frozen section in four (10%) and atypia in 12 (30%). Carcinoma was not suspected in 61% of these specimens until paraffin sections were examined.

Seventy-six per cent (31/41) of the noninvasive carcinomas detected in these contralateral biopsies was LCIS, but only three cases of LCIS were identified on frozen section, while 32% were considered to be atypical and in 58% the specimens were thought to be benign. Ten contralateral biopsies contained IDC (one with LCIS as well). IDC was detected at frozen section in one, two were reported as atypical and in seven the diagnosis was benign.

* The word benign is used throughout the text as a matter of convenience to describe specimens that may have contained any of a variety of non-cancerous histological changes other than those referred to as atypical hyperplasia.

TABLE 3. Type of Residual Carcinoma in Breast After Excisional Biopsy*

Type of Carcinoma in Biopsy (Total Specimens)	Type Residual Carcinoma in Mastectomy Number Breasts†				
	IDC	LCIS	IDC & LCIS	No Residual	Infiltrating
IDC (50)	26	1	4	16	3‡
IDC & LCIS (3)	1	1	1		
LCIS (50)	2	28		18	2§
IFDC¶ (7)	1			2	4

* See legend of Table 1 for explanation of abbreviations. †Nineteen of the 129 patients did not undergo mastectomy. ‡All infiltrating duct type: two near biopsy, one distant. §One each infiltrating lobular at biopsy site and infiltrating duct type outside biopsy quadrant. ¶Each of these patients had IFDC on paraffin section after frozen section reported as IDC. Residual IFDC in four cases was outside the biopsy quadrant; residual IDC in one case was at biopsy site.

Residual Carcinoma in Mastectomy after Excisional Biopsy for Noninvasive Disease

Patients with noninvasive carcinoma only on biopsy. One hundred three mastectomy specimens were available for examination (Table 3). Overall, residual carcinoma was found in 59 or 56% of breasts after the frozen and paraffin sections revealed noninvasive carcinoma. Residual infiltrating carcinoma was found in 3/53 or 6% of breasts with IDC on biopsy. Residual infiltrating cancer was found in two or 4% of patients with LCIS. No patient with residual infiltrating carcinoma in the breast had axillary metastases. The residual carcinoma almost always was of the same type as that found in the biopsy (30/34 or 90% for IDC and 28/32 or 88% for LCIS). Residual carcinoma was found with approximately the same frequency in breasts from pa-

tients with unilateral noninvasive carcinoma and in those who also had contralateral invasive disease. Residual IDC alone was found in 30 cases, of which 20 were limited to the biopsy site and 10 (33%) extended to other quadrants. Persistent LCIS was found in another 30 patients, 24 (80%) of whom had the lesion in quadrants other than the biopsy site. All three patients with both LCIS and IDC in the biopsy had noninvasive carcinoma in quadrants other than the biopsy site.

Patients with invasive carcinoma on paraffin section. The data in Table 3 include seven patients whose paraffin section revealed infiltrating duct carcinoma after the frozen section was reported as IDC. Residual IFDC carcinoma was found at mastectomy outside the biopsy quadrant in four, two had no residual and one had IDC at the biopsy site. None had axillary metastases.

Patients not treated by mastectomy. Nineteen patients did not undergo a mastectomy after a biopsy that contained only noninvasive carcinoma (9-IDC; 10-LCIS) on frozen and paraffin section. Except for two cases reported as intraductal and one as LCIS at surgery, the frozen sections had been reported as not carcinoma (11 cases) or as having significant atypia (5 cases).

Fourteen had bilateral carcinoma. Among them were 12 patients with concurrent contralateral infiltrating carcinoma including four patients who had contralateral axillary metastases. Another patient had contralateral intraductal carcinoma for which a mastectomy was performed while LCIS remained untreated. Prior contralateral mastectomy had been performed in an additional case.

Three of the five patients with unilateral carcinoma not treated by mastectomy had IDC. In one case, no treatment was advised because of advanced age and poor surgical risk. The other two patients elected not to be treated by surgery. Two patients with LCIS also chose not to be treated. In one of these two cases, invasive lobular carcinoma became evident clinically one year later at the biopsy site and a mastectomy was then performed.

TABLE 4. Summary of Literature Describing Residual Carcinoma After Biopsy with Noninvasive Carcinoma

Authors	Type Carcinoma in Biopsy (No. Pts.)	Residual Carcinoma in Breast (Number) %		
		Noninfiltrating	Infiltrating	No Residual
Shah et al. ²⁰	IDC (45)	(21) 47%	(8) 18%	(16) 35%
	LCIS (40)	(26) 65%	(2) 5%	(12) 30%
Carter & Smith ⁵	IDC (38)	(25) 66%	(7) 18%	(6) 16%
	LCIS (49)	(31) 63%	(3) 6%	(15) 31%
Rosen et al. (Present study)	IDC (60)*	(35) 58%	(7) 12%	(18) 30%
	IDC (53)†	(34) 64%	(3) 6%	(16) 30%
	LCIS (50)	(30) 60%	(2) 4%	(18) 36%

* Includes seven patients with IDC on frozen section found to have IFDC on paraffin section of biopsy after mastectomy and three patients with IDC and LCIS in their biopsy.

† Excludes seven patients with IFDC on paraffin section. Includes patients with IDC and LCIS in biopsy.

Patients with Benign Frozen Section and Infiltrating Carcinoma on Paraffin Section

The study population of this investigation was chosen to identify patients most likely to undergo mastectomy with a diagnosis of noninvasive carcinoma, or at least those cases in which a decision on therapy would have been made with this as the only diagnosis. For this purpose we chose patients with a frozen section diagnosis of noninvasive carcinoma who underwent mastectomy before paraffin sections were prepared and those found to have noninvasive carcinoma on paraffin section after frozen section was interpreted as benign

or atypical or noninvasive. We have therefore excluded from the general study those cases in which a frozen section interpreted as benign or atypical was followed by a paraffin section diagnosis of *infiltrating* carcinoma since the presence of infiltration presented a different clinical problem. For the sake of completeness, this group of eight cases will be described briefly in this section.

Five had benign frozen sections followed by a diagnosis of IFDC and one had IFLC after a benign frozen section. Residual carcinoma was found outside the biopsy site in two (1—infiltrating; 1—noninfiltrating). Two patients with atypical duct hyperplasia on frozen section and infiltrating duct carcinoma on paraffin section had residual IDC, which was limited to the biopsy site in one patient but involved other quadrants in another case. None of the eight patients had lymph node metastases.

Discussion

Noninvasive Carcinoma in Biopsy and Residual Carcinoma in Mastectomy

The examination of breast biopsies at the time of frozen section permits only limited sampling.⁴ As a consequence there is a significant possibility that paraffin sections of other portions of the same specimen will reveal carcinoma after the frozen section had been reported as atypical or benign. In a recent review¹⁵ of 556 consecutive breast biopsies examined on frozen section, we reported a false negative rate of 3.2%. Eighty-nine per cent of the carcinoma found in paraffin sections was noninvasive, with the majority *in situ* lobular carcinoma. This disproportionate representation of LCIS probably results from the fact that nonpalpable areas of intraductal carcinoma are more likely to be detected by mammography preoperatively. These foci can then be localized for diagnosis by specimen radiography at the time of frozen section.¹⁹

The present study was limited to an evaluation of cases in which a diagnosis of noninvasive carcinoma was made on frozen or paraffin section. Because we have not tabulated the total number of frozen sections performed during the 23 month period, the exact frequency of false negative reports represented by this series was not available. However, we estimated it to be about 2–3% using as a basis other recent data for breast biopsies performed at Memorial Hospital that were examined at frozen section.¹⁵

Intraductal carcinoma was more likely to be diagnosed or suspected at frozen section than LCIS. On the other hand, invasive carcinoma was not found in paraffin sections of any biopsy reported as LCIS on frozen but there was an invasion in paraffin sections of 20% of

biopsies reported as IDC. Infiltrating carcinoma was detected in three of 50 mastectomy specimens from patients whose paraffin section diagnosis had been IDC and in two of 50 with LCIS at biopsy.

These data become more meaningful when viewed in the context of the diagnosis used as a basis for selecting surgical treatment. Overall, the frozen or paraffin section diagnosis of noninvasive carcinoma proved to be correct after examination of paraffin sections of biopsy and mastectomy specimens in 89% of the 110 patients who ultimately underwent mastectomy. Invasive carcinoma had been detected in seven biopsies after a frozen section reported as noninvasive carcinoma and at mastectomy in an additional five cases reported as noninvasive after examination of frozen and paraffin sections. None of these 12 patients, who constituted 11% of the entire series, had axillary lymph node metastases. Those patients with invasive carcinoma in paraffin sections after a frozen section diagnosis of noninvasive carcinoma had a much greater likelihood of having residual invasive disease at mastectomy (4/7 or 57%) than those with only noninvasive carcinoma at biopsy (5/103 or 5%).

Noninvasive Carcinoma in Biopsy and Multicentricity

Many studies have been conducted to assess the multicentricity of breast cancer by examination of multiple sections of mastectomy specimens.^{6,7,13,17,20,21} From these observations it became clear that overall there was a direct relationship between the size of primary invasive carcinoma and both the overall frequency of multicentricity and the proportion of foci that were invasive.¹⁷ With few exceptions,^{17,21} these investigations have not been carried out in a way that assessed all quadrants in each case of permitted reliable distinctions between tumor remaining in the immediate vicinity of the primary tumor and separate foci in other quadrants.

Few of these reports (Table 4), have dealt with a substantial group of patients whose only lesion on biopsy had been noninvasive carcinoma.²⁰ One study of 40 patients with LCIS at biopsy revealed infiltrating carcinoma in two (5%), noninfiltrating carcinoma in 26 (65%) and no residual in 12 (30%) mastectomy specimens. The results in 45 patients with intraductal carcinoma at biopsy were: infiltrating carcinoma, eight (18%); noninfiltrating carcinoma, 21 (47%); no residual 16 (35%). More recently, Carter and Smith⁵ reported invasive carcinoma at mastectomy in 6.3 and 18.4% of patients with LCIS and IDC, respectively. In yet another study, invasive carcinoma has been found in 1.2% (1/83) mastectomies performed for LCIS at Memorial Hospital between 1951 and 1965.¹⁶ All of these studies in-

cluding our own have employed limited sampling techniques which permit examination of only a small part of the breast. Consequently, the data represent minimal observations and there may even have been microscopic foci of invasive carcinoma in cases we have listed with no residual.

All four studies have consistently detected occult invasion in only about 5% of breasts after a biopsy revealed LCIS. In the present study we were able to determine that invasion occurred outside the biopsy quadrant in one of the two cases in which it was detected. Data from two prior studies^{5,20} listed in Table 4 showed at least a three-fold greater frequency of residual invasive carcinoma when the biopsy showed IDC, but these results were not entirely substantiated in the present investigation. One explanation for this discrepancy may be in differences in study design since Shah et al.²⁰ and Carter and Smith⁵ included only cases with a final paraffin diagnosis of IDC. Furthermore it is difficult in retrospect to determine the extent to which biopsy size or tissue sampling might have differed from the present series. While it seems probable that multicentric invasive carcinoma occurs more frequently in a breast that contains only IDC on biopsy than it does when LCIS is the only lesion, the magnitude of the difference is uncertain.

Method of Biopsy

The importance of considering overall size in assessing the data presented in this and related reports requiring special emphasis. It has been customary for surgeons in this institution to perform "generous" biopsies for most types of lesions under general anesthesia. While this is difficult to quantitate, it commonly means total excision of the mass for which biopsy was performed. In some exceptional cases, a total quadrant may be encompassed by the procedure. In all likelihood entirely different results would be obtained in an institution where highly selective or incisional biopsies were performed. These data may also be directly comparable to results obtained under other circumstances such as biopsy under local anesthesia in an out patient clinic. These factors must be taken into consideration when applying our data to a particular clinical situation.

Predictive Factors

Finally, in this study we have made only a very limited attempt to evaluate features at the time of biopsy that might be useful for predicting the likelihood of multifocal invasive carcinoma after a biopsy revealed only noninvasive disease. However, it would appear from our data that the presence of clinically apparent invasive carcinoma in one breast does not impart a

greater risk of occult invasion in the opposite breast when the two are diagnosed at the same time. Because residual infiltration outside the biopsy quadrant was infrequent, especially when the dominant lesion was LCIS, a large sample will be necessary to evaluate such factors as age at diagnosis and family history of breast cancer.

Implications for Therapy of Noninvasive Breast Carcinoma

Intraductal carcinoma. Data that have been acquired in this and other recent studies strongly support a recommendation for treatment by mastectomy.^{2,4,12,18,22} Residual carcinoma in patients with IDC invariably is of the same histological type and occurs outside the biopsy quadrant in at least a third of cases with persistent disease. Progression to ipsilateral invasive carcinoma occurs in about 40% of patients with IDC not treated by mastectomy.⁴ Furthermore, if IDC were found at the time of frozen section, invasive carcinoma will be detected in further sampling of the biopsy or at mastectomy in 18% of cases.

In most cases, low axillary dissection would be prudent. While occult axillary metastases were not found in this series among patients with intraductal carcinoma or those with microinvasive disease, they have been reported in other studies^{2,5} and we have seen similar cases not included in this investigation. Studies of patients with carcinoma who present with axillary metastases suggest that this is more likely to develop from minimally invasive duct carcinoma than from obscure foci of invasive lobular carcinoma.³ And, discontinuity dissection of level I of the axillary contents ensures complete removal of the axillary extension of breast parenchyma.

Lobular carcinoma in situ. It now appears well established that the risk of occult invasive carcinoma for patients with LCIS is relatively low. Furthermore, residual noninvasive disease is invariably also LCIS that is found in quadrants other than that biopsied in 80% of cases. In this series two patients whose only lesion was LCIS had axillary metastases involving multiple lymph nodes. We have shown elsewhere¹⁸ that the long-term risk of subsequent ipsilateral invasive carcinoma proved to be about 15%. A similar risk of invasion was observed in the opposite breast over the same period. We concluded that no single approach to therapy would necessarily be appropriate for all patients with LCIS. While in some cases careful follow up with mastectomy would be appropriate, ipsilateral modified radical mastectomy and contralateral biopsy offered a prudent approach to treatment for most women until some basis for predicting the future evolution of LCIS in individual patients became available.

The data obtained from this investigation have led us to amend this conclusion with respect to the extent of axillary dissection. The risk of occult invasive disease at the time of diagnosis is not as major a consideration as we had earlier thought it to be and therefore the probability of axillary metastases, while still present, is exceptionally small. On the other hand, it is clear that most patients will retain areas of LCIS in other quadrants even after a wide excisional biopsy and that therefore the risk of progression exists. With these observations it now seems more appropriate to recommend total or simple mastectomy for LCIS as originally suggested by Foote and Stewart, and later by others.¹² Inclusion of at least part of the contiguous low axillary contents is advisable to obtain a sampling of the lymph nodes and to ensure that all breast tissue, including the axillary extension, has been included in the specimen.

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