

Clinically Occult Breast Cancer

Multicentricity and Implications for Treatment

GORDON F. SCHWARTZ, M.D.,* ARTHUR S. PATCHEFSKY, M.D.,† STEPHEN A. FEIG, M.D.,‡
GARY S. SHABER, M.D.,‡ AMORY B. SCHWARTZ§

Mammography as an adjunct to physical examination has led to the detection of a significant number of clinically occult, nonpalpable cancers. In a climate of increasing criticism of radical surgery for any breast malignancy, it is tempting to consider these "earliest" breast cancers as prime candidates for conservative therapy. Sixty-two such nonpalpable tumors have been encountered in a series of 232 breast biopsies performed for radiographically suspicious findings. These included 30 invasive ductal cancers, seven minimally invasive ductal cancers, 20 noninvasive ductal cancers, and five lobular carcinomas-*in situ*. When the mastectomy specimens were examined for evidence of multifocal cancer, 39.6% of the breasts examined demonstrated the presence of foci of invasive or noninvasive ductal or lobular carcinoma in another quadrant of the breast. Additionally, 27.6% of the invasive cancers were accompanied by axillary node metastases in those patients undergoing axillary dissection. Any therapeutic procedure for invasive or noninvasive ductal cancer which does not include total mastectomy may leave behind foci of cancer in the breast, and any procedure for invasive ductal cancer which does not include axillary dissection, regardless of the small size of the cancer, may leave behind microscopic deposits of metastatic cancer in axillary nodes.

AS THE USE OF MAMMOGRAPHY has become ubiquitous throughout the medical community, radiographic findings in the absence of a palpable mass have become recognized as valid indications for breast biopsy. Whether as a screening procedure for asymptomatic women, or as an adjunct to physical examination in the evaluation of specific complaints, mammography has been responsible for the detection of many nonpalpable, clinically occult cancers.

Almost simultaneously, the advocates of less radical forms of therapy for breast cancer have gained more

From the Departments of Surgery, Pathology, and Radiology, Jefferson Medical College, and the Breast Diagnostic Center, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

followers, among both women and primary care physicians, as well as a few surgeons. If conservative treatment is justifiable, it would seem reasonable that these cancers would be those for which such treatment would be most appropriate. It is impossible to deny the attractiveness of any form of treatment which spares the breast, especially if the ultimate result is equivalent to that of radical surgery. It has always been a cruel paradox that mastectomy has been a woman's reward for her diligence in early detection of her breast cancer.

Many studies have reported foci of cancer in the breast remote from the primary lesion.^{2,3,6,8,10,13} Studies of "simulated partial mastectomy" or of whole mount mastectomy specimens have also commented upon this significant finding of multifocal breast cancer.⁹ In most of these reports the primary tumors were palpable, and there are few studies which consider the likelihood of clinically occult cancers being multicentric. If there were a significant incidence of multicentricity, even among these "earliest" breast cancers, perhaps those who advocate only partial mastectomy or other conservative therapy should reconsider their recommendations. Therefore, this study was undertaken to define the incidence of multicentricity in patients whose cancers were identified as clinically occult, detected by mammography only, without the presence of a palpable mass or suspicious thickening in the breast.

Materials and Methods

The patients for this study were culled from the population of female patients referred for mammography at the Thomas Jefferson University Hospital.

Reprint requests: Gordon F. Schwartz, M.D., Department of Surgery, Jefferson Medical College, 1025 Walnut Street, Philadelphia, Pennsylvania 19107.

Submitted for publication: May 4, 1979.

* Professor of Surgery.

† Professor of Pathology.

‡ Associate Professor of Radiology.

§ Summer Research Assistant, Breast Diagnostic Center.

A majority of them were patients enrolled in a breast screening program, but some had been referred by their physician because of breast complaints, or as part of their routine health care. The strict criterion for inclusion, however, was the absence of any physical findings in the breast or axilla which might suggest either benign or malignant disease. For example, a patient found to have an unsuspected breast mass on mammography, which proved to be a cancer, was excluded from this group because an ipsilateral enlarged axillary node had prompted mammography.

Specific radiographic findings mandated the recommendation for breast biopsy. These included any of the following:

- 1) Calcifications suggesting malignancy, because of their shape (punctate, microlinear, or branching), their size (less than 2 mm), their distribution (clustered, grouped along ducts), or their concentration (more than five calcifications per cm²);
- 2) Breast masses with ill-defined edges or nodular contours;
- 3) Stellate shaped breast masses;
- 4) Dominant, well circumscribed masses significantly larger than any other mass in either breast; and
- 5) Areas of abnormal architecture or increased tissue density.

Biopsy was performed by a technique of needle-guided localization to identify the suspicious area precisely before excision, and specimen radiography to insure that the entire area had been removed. We have described this localization technique previously, using only a 22 gauge needle, inserted into the breast under local anesthesia, aiming for the expected site of the lesion.¹¹ Neither radiopaque nor vital dyes, nor special needles, have been necessary to localize and excise the radiographically suspicious areas precisely.

Following needle localization, based upon individual circumstances and the surgeons' preferences, biopsy was usually performed under general anesthesia. Frozen section examination was used as a determinant for immediate further surgery, or a treatment recommendation was deferred until the paraffin sections had been reviewed. (No attempt was made by the authors to influence treatment.) In general, invasive and minimally invasive ductal cancers were treated by total mastectomy with axillary dissection, either radical mastectomy or modified radical mastectomy. Minimally invasive ductal carcinoma was defined as a predominantly intraductal cancer, showing either focal microinvasion below the basement membrane in one or several individual ducts, or up to 10% of the surface of the histological sections showing more advanced stromal invasion. Noninvasive ductal carcinoma was

usually treated by total mastectomy, several patients also undergoing partial axillary dissection, to include the Level I nodes. A few patients in this group refused further treatment altogether. Patients with lobular carcinoma *in situ*, with one exception who underwent total mastectomy, did not have further treatment but were remanded to frequent follow-up examination.

For those patients who underwent mastectomy, the tissues were processed in a detailed manner as outlined by the Pathology Working Group of the National Breast Cancer Task Force.⁷ This usually provided a minimum of four sections from each quadrant of the breast, as well as four sections from the retroareolar area. Axillary nodes were divided into three anatomic groups, using levels defined by the pectoralis minor muscle, or by markers placed by the surgeon during the axillary dissection.

Multicentricity was defined as the presence of invasive or noninvasive ductal or lobular carcinoma in a quadrant other than the quadrant containing the primary cancer. Thus, residual cancer after excisional biopsy, or other noncontiguous foci of cancer in the same quadrant, regardless of histology, were not considered as evidence of multicentricity. If the primary tumor were located deep to the nipple or areola, the lesion was considered multicentric only if additional foci of cancer were demonstrable at least 5 cm beyond the nipple. Similarly, foci of tumor deep to the nipple/areolar complex were considered multicentric only if the primary tumor were at least 5 cm beyond the nipple. (Cancers accompanied by axillary node metastases, in the absence of multicentric foci within the breast as already defined, were not considered multicentric.)

Results

Using the radiographic criteria enumerated, 232 such biopsies were performed at Jefferson between 1973 and January 31, 1979 (Table 1). Within this group were 170 benign lesions, 73.3% of the total number, the vast majority of them demonstrating some variant of epithelial or stromal proliferation commonly grouped under the generic term of fibrocystic disease. Sixty-

TABLE 1. Clinically Occult Mammary Lesions

Diagnosis	Number	Per Cent
Benign lesions	170	73.3
Malignant lesions	62	26.7
invasive ductal	30	12.9
minimally invasive ductal	7	3.0
noninvasive ductal	20	8.6
lobular <i>ca-in situ</i>	5	2.2
invasive lobular	0	—
Total	232	

TABLE 2. Clinically Occult Breast Cancer

Diagnosis	Number	Per Cent
Frankly invasive ductal	30	48.4
Minimally invasive ductal	7	11.3
Noninvasive ductal	20	32.3
Lobular <i>ca-in situ</i>	5	8.0
Invasive lobular	0	—
Total	62	

two malignant lesions were encountered, representing 26.7% of the biopsies (Table 2). Dividing the cancers into subgroups, based upon histology and degree of invasion, almost half, 30 in number, were frankly invasive ductal carcinomas, including eight tubular carcinomas and 22 "garden variety" ductal carcinomas. There were seven minimally invasive ductal carcinomas. Twenty of the biopsies, about one-third of the cancers, revealed noninvasive ductal carcinoma. Two women had bilateral noninvasive ductal carcinoma, one each as synchronous and metachronous lesions. Five women were found to have lobular carcinoma-*in situ*. There were no invasive lobular (small cell) carcinomas. These 62 malignancies occurred in women between the ages of 39 and 75, although the majority were between 45 and 60 years of age.

Discussing first the invasive ductal lesions, 19 of the 30 presented as occult breast masses, and 11 as areas of clustered calcifications. Twenty-nine of the 30 patients underwent mastectomy with axillary dissection, and eight women, or 28% of this group, were found to have axillary node metastases. Four of these eight women had nodes involved only at Level I, three patients a single node and one patient two nodes. However, the other four women were found to have positive lymph nodes at all levels, including the apex of the axilla (Table 4).

Eleven of the breasts with a primary diagnosis of invasive ductal carcinoma, or 37.9%, demonstrated multifocal sites of cancer in the resected breast (Table 3). Three breasts had other foci of invasive ductal carcinoma, seven had foci of noninvasive ductal carcinoma, and one had foci of lobular carcinoma-*in situ*. (Four of the eight breasts with involved lymph nodes had multicentric tumor, but none had a separate invasive focus.)

Each of the seven minimally invasive ductal carcinomas was detected as suspicious calcifications within the breast. All seven women underwent mastectomy with axillary dissection. None had evidence of lymph node metastases. One of these breasts harbored other foci of similar minimally invasive ductal cancer, and three others had multifocal noninvasive ductal carcinoma (Tables 3 and 4). The overall incidence of

multicentricity in these patients with minimally invasive ductal cancer was 57.1%.

There were 20 noninvasive ductal cancers in 18 patients, and 17 of which presented as suspicious calcifications, including both of the women with bilateral lesions. Two patients underwent biopsy because of a suspicious mass seen on the mammograms, and the other patient's biopsy recommendation was on the basis of an asymmetrical density in the breast. In each of these latter three patients, the mass or density was benign, but noninvasive ductal carcinoma was an incidental finding in the specimen. Of this group, 15 women underwent mastectomy, including the patient with synchronous bilateral lesions. Thus, there were sixteen mastectomy specimens for evaluation. (The one patient with metachronous bilateral noninvasive ductal carcinoma underwent mastectomy in 1974, and chose irradiation when her second cancer was diagnosed in 1978.) Twelve of these 16 specimens also included at least the Level I axillary contents, and none had evidence of lymph node metastases. Six of these sixteen mastectomy specimens, or 37.5%, demonstrated evidence of multicentricity, three each with foci of noninvasive ductal carcinoma and lobular carcinoma-*in situ* (Table 3).

The five women with lobular carcinoma-*in situ* underwent biopsy because of suspicious calcifications (three patients) or suspicious masses (two patients). In the latter patients, the masses were benign, and lobular carcinoma-*in situ* was an incidental finding. Only one of these five patients subsequently underwent mastectomy, and there was no residual disease in her breast (Table 3). The other four patients, when advised of the controversial nature of this disease, chose careful follow-up instead of further surgery.

Thus, the overall incidence of axillary node metastases in all 48 patients who underwent mastectomy with axillary dissection was 16.7% (Table 4). However,

TABLE 3. Multicentricity in Clinically Occult Breast Cancer

Primary Diagnosis	Other Foci of Cancer	
Invasive ductal (29)	Invasive ductal	3
	Noninvasive ductal	7
	Lobular <i>ca-in situ</i>	1
	Total 11/29 = 37.9%	
Minimally invasive ductal (7)	Minimally invasive ductal	1
	Noninvasive ductal	3
	Total 4/7 = 57.1%	
Noninvasive ductal (16)	Noninvasive ductal	3
	Lobular <i>ca-in situ</i>	3
	Total 6/16 = 37.5%	
Lobular <i>ca-in situ</i> (1)	None	
Total: 53 mastectomy specimens studied multicentricity in 21/53 = 39.6%		

TABLE 4. Node Metastases in Clinically Occult Breast Cancer

Diagnosis	Number	Per Cent
Invasive ductal	8/29	27.6
Minimally invasive ductal	0/7	0
Noninvasive ductal	0/12	0
Total	8/48	16.7

because only those patients whose primary tumors were frankly invasive had nodal metastases, a more correct assessment should exclude all but these patients from consideration. The incidence of axillary metastases in this group was 28%.

Of the entire group of 53 evaluable breasts, 21, or 39.6%, demonstrated other foci of invasive or noninvasive ductal or lobular carcinoma within the breast, in a quadrant other than the quadrant containing the primary lesion. None of the specimens had a multicentric focus of cancer which was more aggressive histologically than the primary lesion.

Discussion

Depending upon the technique and thoroughness of microscopic scrutiny, multiple foci of cancer in mastectomy specimens are not unusual findings, so that the demonstration of this characteristic in this group of patients is not surprising, per se.⁶ The large proportion, almost 40%, of these apparently "earliest" cancers which were multicentric, is disturbing. Clinically occult, as a descriptive term, must not be equated with "minimal," as this latter term has crept, almost insidiously, into the surgical vernacular. Only two of the 62 cancers in this series were greater than 1.0 cm in diameter, 1.5 and 2.2 cm, respectively, both buried deeply in large breasts, accounting for the inability to palpate them. However, each of the 62 cancers was nonpalpable, even on re-examination, with the positive mammograms at hand, so that they all must be considered "early" breast cancer, from the clinical, if not the biological, point of view. In our own institutional study of Stage I and Stage II breast cancers, using the same criteria to define multicentricity, this incidence was 47%, not an appreciable difference.⁶

An undercurrent of opinion among those physicians who champion the conservative approach of breast cancer has been to minimize the importance of noninvasive breast cancer. If this were valid, this observed incidence of multicentricity would be of no threat to the patient and would not mandate the therapeutic considerations. But we do not feel that this is an acceptable comparison, especially if the multicentric foci are those of invasive or minimally invasive ductal cancer. Additionally, it is not unreasonable to assume that noninvasive ductal cancer

is a precursor of invasive cancer, since about 40% of patients with noninvasive ductal cancer, if not treated by mastectomy, will develop ipsilateral invasive cancer subsequently.¹ Therefore, any treatment which carries a high likelihood of leaving islands of this disease within the remaining breast must be considered inappropriate.

Nine patients in this study had lobular carcinoma-*in situ* as a primary or secondary diagnosis, five in the former category and four other patients with foci of this disease in the resected breast. The long-term follow-up of patients with lobular carcinoma-*in situ* indicates a subsequent risk of about 15% ipsilateral invasive cancer and almost the same chance of contralateral invasive cancer.^{4,10} One may choose to treat these patients without further surgery, but they are at high risk and must be followed carefully and closely. Even if we exclude the diagnosis of multicentric lobular carcinoma-*in situ* from consideration, one-third of our patients had other foci of invasive, minimally invasive, or noninvasive ductal carcinoma. It should also be recalled that our definition of multicentricity is a conservative one, excluding any evidence of malignant foci in the same quadrant as the primary lesion, even if of a different cell type than the original tumor. (If positive axillary nodes are considered in addition to multicentricity, then almost half our patients had either multifocal breast cancer or positive axillary nodes.) This is even more significant when one remembers that all of these lesions were clinically occult.

What are the implications of these findings? The temptation of less than total mastectomy for any malignant lesion of the breast because it is so "tiny" must be tempered by the realization that small must not be equated with inconsequential. At this time, therefore, we do not recommend any surgical procedure less than total mastectomy for invasive or *in situ* ductal carcinoma, regardless of the small size of the primary lesion. Additionally, axillary dissection should be part of the procedure for all invasive cancers, since these small cancers still have about one chance in four of involving the axillary nodes. If irradiation is chosen as an alternative to surgery, because of patient or physician preference, this likelihood of multicentricity must be considered when planning treatment. However, there is little evidence that this treatment modality is effective in eradicating noninvasive breast carcinoma.

Summary

Two hundred thirty-two biopsies have been performed for nonpalpable mammary lesions, detectable by mammography, but not clinically apparent. Sixty-two malignancies were demonstrated within this

group, including thirty invasive ductal cancers, seven minimally invasive ductal cancers, 20 noninvasive ductal cancers, and five lobular carcinomas *in situ*. When mastectomy specimens were examined for evidence of multifocal cancer in quadrants other than that in which the primary was located, 39.6% of the breasts examined demonstrated evidence of multifocal cancer, ductal or lobular, invasive or noninvasive. These findings suggest that any therapeutic procedure for invasive or noninvasive ductal cancer which does not include total mastectomy may leave behind foci of cancer which may be a threat to the patient.

References

1. Betsill W, Rosen PP, Lieberman PH, Robbins GF. Intraductal carcinoma: long-term follow-up after treatment by biopsy alone. *JAMA* 1978; 239:1863.
2. Fisher ER, Gregorio R, Redmond C, et al. Pathologic findings from the national surgical adjuvant breast project (Protocol No. 4): I. observations concerning the multicentricity of mammary cancer. *Cancer* 1975; 35:247-253.
3. Gallager HS, Martin JE. The study of mammary carcinoma by mammography and whole organ sectioning. *Cancer* 1969; 23:855-873.
4. Haagensen CD, Lane N, Lattes R. Neoplastic proliferation of the epithelium of the mammary lobules. *Surg Clin North Am* 1972; 52:497-524.
5. Humphrey LJ: Mammography and the pathologists' cancer in the female breast. *Am J Surg* 1978; 136:285.
6. Patchefsky AS, Shaber GS, Schwartz GF et al. The pathology of breast cancer detected by mass population screening. *Cancer* 1977; 40:1659-1670.
7. Pathology Working Group, Breast Cancer Task Force. Standardized management of breast specimens. *Am J Clin Pathol* 1973; 60:789-798.
8. Qualheim RE, Gall EA. Breast cancer with multiple sites of origin. *Cancer* 1957; 10:460-468.
9. Rosen PP, Fracchia AA, Urban JA et al. "Residual" mammary carcinoma following simulated partial mastectomy. *Cancer* 1975; 35:739-747.
10. Rosen PP, Senie R, Schottenfeld D, Ashikari R. Noninvasive breast carcinoma: frequency of unsuspected invasion and implications for treatment. *Ann Surg* 1979; 189:377-382.
11. Schwartz GF, Feig SA, Patchefsky AS. Clinicopathologic correlations and significance of clinically occult mammary lesions. *Cancer* 1978; 41:1147-1153.
12. Schwartz GF, Patchefsky AS, Feig SA. Multicentricity of clinically occult mammary cancer: implications for treatment. Presented at the annual meeting of the Society of Surgical Oncology, 1979.
13. Shah JP, Rosen PP, Robbins GF. Pitfalls of local excision in the treatment of carcinoma of the breast. *Surg Gynecol Obstet* 1973; 136:721-725.