Mammographically Detected Breast Cancer

Nonpalpable Is Not a Synonym for Inconsequential

Gordon F. Schwartz, M.D., M.B.A.,† David L. Carter, M.D.,†*
Emily F. Conant, M.D.,‡§ Francis H. Gannon, M.D.,‖
Gerald C. Finkel, M.D.,‖¶ and Stephen A. Feig, M.D.,‡§

Background. Needle-guided breast biopsy has become a regularly recommended procedure to excise nonpalpable, questionable breast lesions detected by mammography. Whether cancers detected in this manner have a more favorable outcome than those detected by clinical examination is not clearly documented.

Methods. To address questions about the biology of mammographically detected cancer and likelihood of axillary node metastasis, as well as the accuracy of screening mammography, data from 3752 needle-guided breast biopsies and 1175 nonpalpable breast cancers were reviewed.

Results. Between 1974 and 1992, 3752 needle-guided biopsies were performed in 3441 women for nonpalpable breast lesions. Benign disease was disclosed in 2575 (68.7%) biopsies and malignancy in 1175 (31.3%). Of 1130 malignancies, 61.8% were invasive carcinomas; 4.8% were microinvasive ductal carcinomas; 28.5% were ductal carcinomas in situ; and 4.8% were lobular carcinomas in situ. Axillary dissection in 558 patients with invasive carcinoma revealed that 27.1% had at least one positive axillary node. Of patients with invasive cancers presenting as nonpalpable calcifications alone, 27.5% had at least one positive axillary node.

Conclusions. More than one fourth of patients with nonpalpable, invasive cancer in this series had axillary node metastasis. Therefore, axillary dissection is an important treatment consideration for all patients with invasive carcinoma, despite technique of detection. Ductal carcinomas in situ detected as limited calcifications do not require axillary dissection. In this study, 31% of biopsies proved the presence of malignancy, an acceptable and appropriate benign-to-malignant ratio. *Cancer* 1994; 73:1660–5.

Key words: nonpalpable breast neoplasms, mammography, clinically occult breast neoplasms, screening, ductal carcinoma in situ, in situ cancer.

The ubiquitous use of mammography for the screening of asymptomatic women as well as in the evaluation of specific symptoms of breast disease has been a major advance in the early detection of carcinoma of the breast.[1] Notwithstanding the current imbroglio about mammography in young women,[2] the merits of screening mammography, at least for women older than 50 years, have become almost universally accepted. The only unresolved controversies are the age at which mammography should begin and the appropriate intervals between screenings. More and more women are advised to undergo breast biopsy based on these often barely perceptible radiologic findings. Thus, the diagnosis of malignancy is often made on the basis of these nonpalpable findings, using the procedure popularly known as "needle-guided biopsy" to localize and excise small mammographic abnormalities. It is often assumed that finding a cancer too small to feel, detected only by mammography, automatically implies a better outcome.

The ability of mammography to detect these tiny areas of abnormality and the surgical safety of breast biopsy, because it is an outpatient procedure that may be performed during local anesthesia, weigh the risk–benefit ratio strongly in favor of surgery. The proportion of such biopsies that actually disclose malignant

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From the *Department of Surgery, Jefferson Medical College, the †Surgical Service, the ‡Department of Radiology, Jefferson Medical College, the §Breast Imaging Center, Thomas Jefferson University Hospital, the ‖Laboratory of Surgical Pathology, and the ¶Department of Pathology, Jefferson Medical College, Philadelphia, Pennsylvania.

Address for reprints: Gordon F. Schwartz, M.D., M.B.A., Jefferson Medical College, 1015 Chestnut Street, Suite 510, Philadelphia, PA 19107–4305.

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disease ranges from less than 10%[3] to more than 30%,[4] reflecting the combined skills of the radiologist and the surgeon. However, it is more essential than ever before to address the costs incurred by mammographic screening. Recommendations for biopsy based on a questionable mammogram commit the patient to a surgical procedure. In addition to the formidable emotional response that breast biopsy elicits from the patient, too low a benign-to-malignant ratio consumes resources that could be better used elsewhere.

How can a balance be achieved between the need for the careful evaluation of the patient with a "suspicious" mammogram and concern for the appropriate consumption of increasingly precious resources? Moreover, what is the biologic character of these tiny malignancies? Are they less likely lethal because they are small? Is the term "minimal" ever an apt description for them?[5] To address these questions, we have reviewed data concerning 1175 cancers in 3752 needle-guided biopsies performed for questionable roentgenographic findings.

Patients and Methods

The specific radiographic findings that usually provoke a recommendation for breast biopsy have been established and are well described.[6] In the presence of one of these indications, needle-guided biopsy was performed using a technique we have described previously.[7] Since 1989, we have generally used a commercially available, hook-wire needle inserted aseptically into the breast while the breast is held firmly in an alpha-numeric grid device. The needle is left in place as a stiffener, not withdrawn, and the patient and her post–needle placement radiographs go to the operating room together.

Using *local* anesthesia (lidocaine *0.25%* with 1:400,000 epinephrine), usually without any supplemental sedation, an incision is made overlying the questionable area and a tunnel created through the breast aiming at this area. Precise positioning of the needle by the radiologist minimizes the volume of tissue removed. When a mass is the reason for the biopsy, it may often be palpated once the breast is open: if benign by palpation and inspection, it may be removed with only a small rim of contiguous normal breast. When there is any question whatsoever about the identity of the mass removed and the mammographic finding that precipitated the decision for biopsy, specimen radiography is mandated.

It is essential, however, to send *all* specimens for specimen radiography when *calcifications* are the questionable finding that provoked the recommendation for biopsy. The sterile field is not violated until the specimen radiograph ensures that the excised tissue contains the area of concern. Specimens containing calcifications usually are not sent for frozen-section examination; they are fixed, embedded, and step-sectioned because of their small size and nonuniform character. As the measurement of hormone receptors on formalin fixed tissue has become available, paraffin blocks of cancers formerly too small to undergo these studies are sent for estrogen and progesterone receptor assays, as well as prognostic markers such as Ki-67. In general, therapeutic recommendations are postponed until the paraffin sections are reviewed and, in the patients with cancer, metastatic workup is completed.

Treatment of breast cancer has evolved continually since the first patient underwent needle-guided biopsy in 1974. Virtually all patients with invasive (ductal or lobular) or microinvasive ductal cancer treated before 1979 underwent mastectomy with complete axillary dissection; since then, limited operative procedures and irradiation have been used with greater frequency. Before 1985, our surgical standard for patients with invasive cancers undergoing irradiation as an alternative to mastectomy was local excision and Level I axillary dissection, and since then has been Levels I and II dissection. (Patients with nonpalpable tubular or colloid/mucinous carcinomas still undergo Level I dissection only.) The average number of nodes recovered from axillary dissections (I, or I and II) was 24.

Before 1978, patients with ductal carcinoma in situ (DCIS) were usually treated in the same manner as those with invasive carcinoma. Between 1978 and mid-1986, irradiation became an option for patients with localized DCIS, but axillary dissection was part of the treatment. Since then, axillary dissection generally has not been performed in patients with *subclinical* DCIS. In addition, since 1978, selected patients with nonpalpable, *subclinical* DCIS have been treated by excision and surveillance alone, without further surgery or irradiation.[8] Although for this report the cases of DCIS detected were not subdivided by the distribution of calcifications throughout the breast, patients with DCIS that fit the criteria for the surveillance option did not undergo axillary dissection *or* irradiation *or* mastectomy. Thus, patients with DCIS who did undergo axillary dissection, usually with mastectomy, were patients with mammographically detected, malignant-appearing calcifications throughout their breast. (These cases, fortunately uncommonly encountered, are best described as having no invasive carcinoma in any of the sections examined; they are not similar to cases of the more limited DCIS.[8]) The patients with lobular carcinoma in situ did not undergo further treatment after the diagnosis was established, but they are being followed closely.

Mastectomy specimens (and axillary node dissections) were processed in the surgical pathology labora-

Table 1. Malignancies Encountered in 3752 Needle-Guided Biopsies; Histology of Malignancy in 1130 Reviewed Cases (1130/1175 = 96.2%)

Type	No.	%
Invasive carcinoma, duct or lobular	699	61.8%
Microinvasive ductal cancer	54	4.8%
DCIS	322	28.5%
LCIS	54	4.8%
Other (malignant carcinoid)	1	0.08%
Total	1130	—

DCIS: ductal carcinoma in suto; LCIS: lymphoid carcinoma in suto.

tory as outlined by the Pathology Working Group of the National Breast Cancer Task Force.[9] Axillary nodes were divided into three anatomic groups using levels defined by the pectoralis minor muscle, with marking sutures sewn into the tissues during mastectomy. As irradiation became more often the option chosen as an alternative to mastectomy, the axillary dissection was performed through a separate incision, and the node groups were subdivided by the surgeon at the operating table and submitted separately to the pathologist. In this manner, the number and distribution of involved nodes could be accurately assessed.

The increasing use of irradiation as an alternative to mastectomy for patients with invasive carcinomas, and the selection of patients with subclinical DCIS for treatment by excision and surveillance alone, have made it all but impossible to pursue studies of multicentricity reported previously.[6] In general, the only patients who currently undergo mastectomy for nonpalpable invasive carcinomas are those with multiple, widespread calcifications indicative of multicentricity. Virtually all others are treated by irradiation.

Results

Between early 1974 and December 31, 1992, 3752 needle-guided biopsies were performed in 3441 women. Benign diseases were encountered in 2575 (68.7%) specimens; malignancy was detected in 1175 (31.3%). Arbitrarily, the patients were divided into three groups: (1) those undergoing biopsy before July 1986; (2) those undergoing biopsy between July 1986 and July 1991; and (3) those undergoing biopsy between July 1991, and December 31, 1992. Consistency in the percentage of biopsies that were positive for malignancy was remarkable: 330 of 1130 = 29.2%, 621 of 1910 = 32.5%, and 225 of 710 = 31.7%, respectively. Of this total number, 1130 (96.1%) could be further categorized microscopically (Table 1). There were 699 invasive carcinomas, either of ductal or lobular origin (61.8%), 54 microinvasive ductal carcinomas (4.8%), 322 DCIS (28.5%), 54 specimens showing lobular carcinoma in situ only (4.8%), and one malignant carcinoid (0.1%). The term "microinvasive" has been defined previously, and our definition parallels that used by Schwartz et al.[8] and Solin et al.[10] One phyllodes tumor encountered was included in the benign group.

Table 2. 558 Patients With Invasive Carcinomas and Axillary Dissection

Node status	No.	%	
Negative	407	72.9%	—
Positive	151	27.1%	—
Node status of the positive node patients with positive nodes		**No.**	**%**
Level I, 1 node +	—	50	33.1%
Level I, 2–3 nodes +	—	33	21.8%
Level I, 4 or more nodes or multiple nodes at all levels positive	—	57	37.7%
No information	—	11	7.3%

Of the group of patients with invasive cancers, 558 (79.8%) underwent an operative procedure (either mastectomy or local excision and irradiation) that included axillary dissection (Table 2). In 407 (72.9%) of this group, the axilla was negative for metastatic disease, but 151 (27.1%) patients had at least one positive axillary node. Fifty of this latter group had a single positive node at Level I (33.1%); 23 (21.8%) had two or three positive nodes at Level I; 57 (37.7%) had four or more positive nodes at Level I or involved nodes at Level II or Level III. Seven patients with invasive carcinoma (0.6%) were found to have metastatic disease (Stage IV) at the time of initial diagnosis.

We have further separated the invasive cancers with axillary dissections into two groups—those detected as nonpalpable masses, masses with internal calcifications, or areas of parenchymal distortion, versus those detected merely as areas of clustered calcifications. Of the 558 total axillary dissection specimens, 391 were from patients in the former groups and 167 were from patients with calcifications only as the means of detection (Table 3). Surprising was the observation

Table 3. Node Status Versus Mammographic Findings

	Positive nodes		Negative nodes	
Mammographic findings	*No.*	*%*	*No.*	*%*
Mass with or without calcifications	105	26.9%	286	73.1%
Calcifications alone	46	27.5%	121	72.5

that, of the group who presented with clustered calcifications only, 46 of 167 (27.5%) had at least one positive axillary node. In addition, three of the seven patients whose disease was Stage IV at diagnosis had only calcifications as the presenting sign of disease. Of the remaining patients with invasive carcinoma, detected as a mass, a mass containing calcifications, or parenchymal distortion, who underwent axillary dissection, 105 of the 391 (26.9%) had at least one positive axillary node. Four of the seven women with Stage IV disease were from this group.

Of the 109 patients with microinvasive breast cancer *or* DCIS who underwent axillary dissection (usually Level I only) as part of their treatment (usually mastectomy), a single patient had two positive axillary nodes. She presented with widespread multiple calcifications and underwent mastectomy with full axillary dissection. The invasive carcinoma was never found despite multiple step-sections through the mastectomy specimen. The other 108 patients with microinvasive cancers or DCIS only who underwent axillary dissection had negative nodes.

Discussion

If it is tempting to consider nonpalpable cancers less threatening because of their small size and their "accidental" discovery, this would seem to be especially true for cancers detected as small areas of calcifications but not yet forming an actual mass. These are often invisible even to the surgeon when the area is exposed and excised; only the specimen radiograph ensures that the questionable area has been removed.

The term "minimal" has crept into the medical vernacular to describe both noninvasive carcinomas and those invasive carcinomas that are 0.5 cm or less in diameter.[5] We previously challenged this assumption that a small, but invasive, carcinoma is not life-threatening, based on our prior observation that the incidence of axillary node metastasis was significant, even for the smallest of cancers.[10] The current study confirms that impression.

The term "minimal" is not an appropriate adjective to describe invasive cancer of any size. More than one fourth of the patients in this series who had invasive carcinomas had at least one positive axillary node at the time the axilla was dissected. This is not substantially different from the proportion of patients with microscopically positive nodes whose cancer is discovered as a palpable mass up to 3 cm diameter and who have no clinical evidence of involved axillary nodes (N0).[11] This group of cancers detected by mammography is large enough to permit us to separate those that are in situ (noninvasive) from those that are invasive. This is extremely important, because subclinical, mammographically detected DCIS is virtually never accompanied by axillary node metastasis. Our single patient with nonpalpable "DCIS" who had two positive axillary nodes was unusual because of the widespread distribution of the calcifications in her breast. It is reasonable to consider hers an invasive carcinoma despite inability to prove the presence of invasion *in the sections reviewed.*

The persistent allegations that DCIS may be accompanied by axillary lymph node metastasis should be challenged. These combined series often include clinically evident masses and widespread, malignant-appearing calcifications, as well as subclinical cases of DCIS detected as small (2–3 cm in diameter) areas of mammographic microcalcifications.[12] We do not believe that these all are the same disease; it is essential to distinguish among them, because therapeutic recommendations may differ. A palpable mass that does not disclose invasion in any of the sections studied and is, therefore, called "DCIS" should be treated in the same manner as any invasive cancer of the same size. This recommendation is valid also for patients whose mammograms disclose malignant-appearing calcifications widely scattered through more than one quadrant of the breast. These patients also should have at least Level I axillary dissection as part of their treatment. Patients with subclinical DCIS detected as areas of calcifications confined to one segment of the breast who choose irradiation or mastectomy do not need axillary dissection. The likelihood of a positive node is remote.

As reports of nonpalpable malignancies accumulate, cases of DCIS should be separated from those of invasive carcinomas with regard to axillary node metastasis. The same is true for patients who have DCIS found incidentally when a biopsy is performed on the basis of a nonpalpable mass (and the mass proves to be benign). Since 1978, we have not treated any patient with DCIS as an incidental finding other than by local excision and surveillance, and none has yet suffered recurrence.

With respect to noninvasive cancer, the detection of DCIS has become a major benefit of screening mammography. In this study, more than one fourth of the malignancies encountered were DCIS. Although the 54 cases of lobular carcinoma in situ (lobular neoplasia) are included in the tally of malignancies encountered, we recognize the controversy about this disease; these cases could be deleted from the data without significance.

The biology of DCIS, as well as its treatment, especially in those patients in whom it is detected as truly minute areas of calcifications, is controversial and enigmatic. However, differences in the nuclear morphology of some of these tiny lesions, even those called "come-

Table 4.

First author	No. biopsies	% malignant
Schwartz (current report)	3752	31%
Wilhelm[14]	1464	18%
Franceschi[15]	1144	24%
Silverstein[16]	1014	20%
Thompson[17]	548	24%
Papatestas[18]	475	31%

docarcinoma," are striking. Our own studies and those of others certainly imply the evolution of further in situ or invasive cancers from at least some of them, even if it may be a minority.[7,13] The recognition of DCIS is important; current limitations of knowledge about treatment does not mitigate the need for diagnosis.

With respect to the accuracy that can be achieved by careful cooperation between surgeons and radiologists, the proportion of biopsy samples that proved to be malignant in this large, 18-year, series was high: 31%. The percentages of malignancies detected in other recent reports of at least 400 needle-guided biopsies are summarized in Table 4.[14–18] These range from 18% to 31%. Smaller series have reported a wider range of positive biopsy samples.[3,4] The techniques of mammography have improved sufficiently that recommendations for breast biopsy now are commonly made for subtle areas of microcalcifications that require magnification mammograms to confirm their presence.[19] Because alleged failure to diagnose breast cancer is unfortunately a leading cause of medical malpractice claims, liberal biopsy recommendations for tiny areas of calcifications address concerns about liability.[20,21] Whether the biopsy procedure could have been avoided safely is seldom a consideration, and women rarely complain about biopsies that prove the presence of benign disease.

However, the costs incurred by screening mammography include the professional and hospital charges for the further evaluation (ultrasound, surgical consultation, and/or biopsy) of patients whose mammograms are considered "suspicious." What proportion of these women might be spared the additional costs and the formidable emotional travail of breast biopsy by more precise interpretation of their radiographs and more liberal use of 6-month follow-up radiographs as an alternative to immediate biopsy? Second opinions are already part of surgical practice; perhaps they should be introduced to radiologic practice as well.[22] We are convinced that patients are not jeopardized by a reasonable delay to substantiate the need for biopsy, and many biopsies can be avoided if the areas in question do not change over time.[23]

The detection of cancer in the biopsies performed for mammographic abnormalities correlates well with the incidence of cancer encountered in biopsies performed for clinical findings. In the experience of the senior author (G.F.S.), whose clinical practice is restricted to breast disease, the ratio of benign to malignant biopsies is 2.5 to 1, based on clinical suspicion alone; the 31% yield for the needle-guided biopsies described in this report is about 2.3 to 1, which is quite comparable. In the last 2 years alone, the experience of the senior author in patient evaluation for needle-guided biopsy yielded malignancy in 40.7% of biopsies, a benign-to-malignant ratio of about 1.5 to 1. Even acknowledging that mammography can detect cancers that are smaller than those usually detected by clinical examination, an appropriate current goal for the ratio of benign to malignant findings in biopsies performed for nonpalpable lesions should be at least the same as that for palpable lesions. Until this target (± 30%) can be uniformly achieved, this should temporarily satisfy the nonphysician guardians who will increasingly adjudicate the cost efficiencies of health care delivery. Our data and those of others indicates this is a reasonable goal.[24] It is an intriguing observation that these overseers of health care, as they seek to lower expenses, fail to grasp the simple concept that lowering the incurred costs of screening mammography by greater accuracy in interpretation argues for an allocation of greater resources, not less, to this initial step in the diagnostic process. It will be here that the greatest economies can be achieved. It seems ludicrous that managed care plans, for example, often negotiate for the cheapest mammograms, often provoking a greater number of expensive biopsies, when they could instead devote appropriate resources to eliminate the need for many of these biopsies altogether.

A higher than expected proportion of women with nonpalpable invasive cancers still have axillary node metastases when detected, so that small must not be confused with inconsequential. However, the argument for screening mammography is reinforced by its detection of many cancers when they are biologically less formidable, i.e., noninvasive and not yet clinically apparent. It is this group of women for whom the term "minimal" remains appropriate. Until the millennium of prevention arrives, we remain convinced that screening mammography, combined with clinical examination, is the major advance in the early detection of breast cancer in this generation.

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