
Nonpalpable Invasive Breast Cancer

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The use of mammography has resulted in 1464 breast biopsies for nonpalpable abnormalities at the University of Virginia in the 10 years 1980 to 1989. Two hundred sixty-four cancerous lesions (18%) were found. One hundred seventy-eight of these (67%) were *in situ* lesions. Invasive cancer (86 of 264 lesions or 33%) forms the basis for this report. Mammographic findings leading to biopsy were a mass in 61 of 86 cases (71%), microcalcifications in 23 of 86 (27%), or both in 2 of 86 cases. Histologic subtypes were infiltrating ductal (63 of 86), infiltrating lobular (14 of 86), and other infiltrating (9 of 86). Mastectomy was performed in 71 of 86 lesions (82%), lumpectomy/radiation in 14 of 86 (16%), and lumpectomy alone in 1 of 86 lesions. Division of the tumors into size with nodal status revealed 19 of 86 lesions (22%) less than 0.5 cm with 0 of 14 positive nodes. Thirty-nine of eighty-six lesions (46%) measured 0.6 to 1.0 cm with 10 (26%) positive nodes. Twenty-eight of eighty-six lesions (32%) measured more than 1.0 cm with 8 of 28 (28%) positive nodes. Nodal status is unknown for eight patients. Overall 18 of 78 lesions (23%) had positive nodes. Median follow-up is 44 months. Disease-free survival rate is 92% (79 of 86 patients) and overall survival rate is 94% (81 of 86 patients). Six of seven recurrences occurred in node-positive patients. For those with negative or unknown nodes, the disease-free survival rate is 98% (67 of 68 patients). These findings emphasize the benefit of early detection of breast cancer through the use of mammography.

SCREENING FOR BREAST cancer by the use of mammography has resulted in the detection of an increased number of noninvasive cancers as well as the discovery of small invasive lesions. These nonpalpable invasive cancers unfortunately demonstrate a significant number of nodal metastases and therefore the term 'minimal breast cancer,' as described by Gallager and Martin in 1971,¹ should not be applied to these lesions. It is the purpose of this paper to evaluate a series of nonpalpable

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invasive breast cancers diagnosed at the University of Virginia from 1980 to 1989 and correlate the characteristics of tumor size, histology, and nodal status with outcome. Recommendations regarding management can be made as a result of this evaluation.

Materials and Methods

Patients

From 1980 to 1989 at the University of Virginia, 1464 women had evaluation and biopsy of clinically occult nonpalpable breast lesions. All lesions were excised using Kopan's wire mammographic directed needle localization as previously described.² Two hundred sixty-four were malignant, with 177 (67%) of them determined to be *in situ* lesions (ductal carcinoma *in situ* or lobular carcinoma *in situ*). Invasive cancer was present in 86 patients (33%). These women with invasive cancer form the basis of this study.

Mammography and Pathologic Status

Mammography was performed for the entire study period with film screen techniques. Mammograms of all study patients were reviewed and the predominant finding leading to biopsy classified as a mass or density, clustered microcalcifications, or both. The pathologic status of all cases was reviewed to confirm the diagnosis of invasive cancer. Tumor size in this study is defined as the maximal diameter as measured grossly or histologically. Nine cases were excluded from detailed histopathologic analysis because the slides from these cases were unavailable for review.

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Follow-up

Follow-up status and treatment decisions were reviewed retrospectively. Data were obtained from hospital and physician charts and tumor registry information. Most of the patients are followed regularly in the Surgical Oncology Clinics at the University of Virginia (UVA). For those currently not followed at UVA, follow-up status was determined by direct patient and physician contact. Follow-up is expressed in months from initial diagnosis to date of last known contact.

Results

Patient Characteristics

Invasive cancer was present in 86 of 1464 (6%) nonpalpable lesions. Age ranged from 36 to 83 years (median, 62 years). Mammographic findings that prompted biopsy were clustered microcalcifications in 23 (26%), solid mass or density in 61 (71%), and both in 2 (3%) (Table 1). Local management of the breast was total mastectomy (simple or modified radical) in 71 (83%), wide excision plus radiation therapy in 14 (16%), and wide excision alone in 1. Wide excision plus radiation was used more widely in recent years. Axillary lymphadenectomy (level I/II) was combined with mastectomy or lumpectomy in 78 patients (90%). Factors leading to the decision not to perform axillary lymphadenectomy included advanced age, physician recommendation, and patient refusal.

Histology showed infiltrating ductal carcinoma in 63 patients (73%), infiltrating lobular in 14 (16%), and other infiltrating in 9 (10%). Tumor size ranged from 0.2 to 2 cm. Overall 18 of 86 women (20%) with nonpalpable invasive breast cancer had nodal metastases. Table 2 outlines the relationship of tumor size and nodal involvement.

TABLE 1. Characteristics of 86 Patients with Nonpalpable Invasive Breast Cancer

Characteristic	n
Mammographic finding	
Clustered microcalcifications	23
Mass/density	61
Both	2
Histology	
Infiltrating ductal	63
Infiltrating lobular	14
Other infiltrating	9
Local Therapy	
Total Mastectomy (simple or modified radical)	71
Lumpectomy/radiation	14
Lumpectomy alone	1
Axillary dissection (with lumpectomy or mastectomy)	78

n = 86.

TABLE 2. Tumor Size and Axillary Nodal Status in 86 Women with Nonpalpable Invasive Breast Cancer

Tumor Size	Number Total	Number of Axillary Dissection	Number of Positive Nodes
<0.5 cm	19	14	0
0.6–1.0 cm	39	36	10 (26%)
>1.0 cm	28	28	8 (28%)
Total	86	78	18 (21%)

Nineteen women had tumors less than 0.5 cm, of whom 14 had axillary dissection and none had nodal metastases. Thirty-nine women had tumors measuring 0.6 to 1.0 cm, of whom 36 had node dissection and 10 (26%) had positive nodes. All 28 with tumors larger than 1 cm had node dissection with 8 (28%) of them testing positive.

Follow-up

Follow-up ranges from 6 to 120 months (median, 44 months). Seventy-nine of eighty-six patients remain free of disease at last follow-up. Tumor recurred in seven women. Six of seven recurrences occurred in women with nodal metastases at the time of diagnosis. Time to recurrence from time of diagnosis ranged from 8 to 100 months (median, 14 months). Recurrence based on nodal status is outlined in Table 3. The disease-free survival rate for women with known negative or unknown axillary nodes is 98% (67 of 68 women) and for those with positive nodes the rate is 67% (12 of 18 women). The single disease event in the node-negative group was the development of a rapidly progressive contralateral new primary breast cancer 15 months after diagnosis of the original lesion.

Adjuvant therapy was not administered to most of the women with negative nodes. One premenopausal woman with negative nodes was treated with adjuvant combination chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) and four postmenopausal women received adjuvant tamoxifen.

Discussion

This study outlines the findings in a group of women with invasive breast cancer detected by mammography while the lesion was nonpalpable. The data raise a number

TABLE 3. Follow-up Status for Women with Nonpalpable Invasive Breast Cancer

Node Status	Total	Number Recurred	% DFS*
Negative	60	1	98%
Unknown	8	0	100%
Positive	18	6	67%

* Median follow-up, 44 months.

TABLE 4. Relative Incidence of In Situ (LCIS or DCIS) and Invasive Cancers in Series of Biopsies of Mammographically Detected Clinically Occult Breast Lesions

Study	n	In Situ Lesions (%)	Invasive Lesions (%)
Tinnemans ¹²	151	34	66
Schwartz ¹³	330	31	69
Papatestas ¹⁴	149	40	60
Symmonds ¹⁵	72	18	82
Univ. of Virginia*	264	67	33

* Reported in present series.

of issues including the effectiveness of mammography in reducing breast cancer deaths, the need to biopsy many benign lesions, and the treatment of these women, including the use of axillary dissection and adjuvant therapy.

The report by Egan³ in 1960 spurred the increase of mammography for breast cancer detection, leading to the National Breast Cancer Demonstration Detection Project in the 1970s.⁴ Long-term results showed that 42% of cancers in women older than 50 years were found by mammography alone and that the mortality rate was decreased by 27% for screened women. Other studies demonstrated a survival benefit for women who undergo periodic breast cancer screening, including Henson's⁵ recent report of decreased mortality rate in women in the Bay area since 1973 attributed to screening. Smart⁶ recently published a complete review of the role of mammography in breast cancer.

The detection of these cancers requires that many benign lesions be biopsied. The incidence of positive biopsies for suspicious mammographic findings ranges from 15% to 30%.⁷ The high rate of negative biopsies has prompted some to question screening programs and cost-benefit studies have been recently presented.⁸ Techniques to reduce the number of negative biopsies are under active investigation. The most promising is stereotactic localized fine-needle aspiration biopsy. Certainly the high rate of negative biopsies can be justified if there is improved outcome for women with mammographic-detected breast cancer.

Interestingly the high negative biopsy rate for nonpalpable lesions has seldom been compared to that of palpable lesions not amenable to cytologic evaluation. In our institution 1464 biopsies for suspicious mammograms yielded 264 cancers (18%). In the period 1988 to 1989, the positive-biopsy rate for palpable lesions not amenable to fine-needle cytology was 20%. Lay⁹ reported a 15% positive-biopsy rate for palpable lesions at the University of Florida. Spivay¹⁰ and Shapiro¹¹ reported similar findings.

Active breast screening has increased the number of cancers detected by mammography and has changed the distribution of cancer types. From 1968 to 1978, 4% of

cancer at UVA were detected by mammography compared to 45% from 1988 to 1989. Of 264 nonpalpable cancers in this series, fully two third were *in situ* lesions. This compares to palpable lesions, of which 90% are invasive. Others have also reported a higher proportion of *in situ* lesions in recent series (Table 4). The preponderance of *in situ* lesions seen in our series may be explained by the 18% positive-biopsy rate compared to 29% to 31% in others.¹²⁻¹⁴

We found that most lesions that proved invasive appeared as a mass or density on mammogram. In many series clustered microcalcifications are the more common finding for malignancy. This difference may be due, in part, to the fact that this series only includes invasive cancers. *In situ* lesions are more consistently associated with microcalcifications. Many series of mammographic findings group invasive and *in situ* lesions together.

The histologic makeup of this series is not unusual, with 73% infiltrating ductal cancer. It is of particular interest that there is no difference in histologic type or nuclear grade in those lesions measuring less than 1 cm. This supports the notion that these are truly invasive cancers that differ from larger lesions in size only.

In this series 21% of women had nodal involvement. Other studies also report a significant incidence of nodal metastases in nonpalpable invasive breast cancer (Table 5). The incidence is 0% to 7% for lesions smaller than 0.5 cm and up to 25% for those measuring 0.6 to 1.0 cm. These figures demonstrate that invasive cancer can be found by mammography while it is small and localized to the breast. The data also emphasizes that small invasive cancers metastasize with distressing frequency and that invasive cancer cannot be labeled 'minimal breast cancer' on the basis of size alone.

Most of the women in this group were treated with mastectomy. Multiple factors entered into the decision process. The incidence of mastectomy for these small lesions is high but corresponds with other reported series.¹⁴⁻¹⁷ Breast-conserving surgery was more broadly applied in the latter years of this series. Level I/II axillary

TABLE 5. Incidence of Nodal Metastases in Women with Mammographically Detected Invasive Breast Cancer from Reported Series

Study	Inclusion Criteria	n	Node Positive (%)
Schwartz ¹³ Tinnemans ¹²	Nonpalpable	167	33
	≤0.5 cm	13	7
	0.6-1.0 cm	24	12
Ciatto ¹⁶	≥1.0 cm	44	29
	≤1.0 cm	34	2
	≥1.0 cm	79	18
Univ. of Virginia	≤0.5 cm	19	0
	0.6-1.0 cm	39	26
	≥1.0 cm	28	28

dissections were performed in 90% of these women, with the findings outlined above. Because of the implications for postsurgical therapy and survival, and because the incidence of nodal metastases is significant, we endorse performing level I/II axillary node dissection in nonpalpable invasive breast cancer.

The survival of these women correlated with nodal status. With a relatively short median follow-up period of 44 months, 98% of those with negative or unknown nodes were disease free. Recurrence in 33% of women with positive nodes corresponds to expected figures for node-positive disease. This underscores the seriousness of the disease regardless of tumor size or method of detection.

The high disease-free survival (DFS) rate for node-negative or unknown nodal status women corresponds closely with other recently reported series. Tinnemans¹² and Ciatto¹⁶ had 90+% DFS at 10 years. Carter¹⁸ reported 98% 5-year DFS, Rosen¹⁷ 86% 20-year DFS, and Rosner¹⁹ 96% 7-year DFS. Node-negative women in general do worse in these series of small lesions. A recent analysis of node-negative breast cancer by Henderson,²⁰ including the control arms of randomized studies of adjuvant therapy, showed that 5-year DFS is only 65% to 75% for all node-negative women. Studies of adjuvant therapy have shown benefit for women with negative nodes who receive adjuvant therapy. The findings in this paper question whether data from these controlled series can be extrapolated to all women with node-negative invasive breast cancer. This study and others demonstrate that adjuvant therapy is not necessary for the subset of women with node-negative invasive breast cancer whose tumors are small and nonpalpable.

Summary

Mammographic screening for breast cancer detects nonpalpable invasive breast cancer as well as a high proportion of *in situ* lesions. Detecting cancer at this small size results in lower breast cancer mortality rates. The presence of axillary node metastases in more than 20% of women with nonpalpable invasive breast cancer supports the need for axillary dissection and emphasizes that

this is not minimal breast cancer. The correlation of size and node status with excellent survival rates identifies a subset of women with node-negative breast cancer who are not candidates for adjuvant therapy.

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DISCUSSIONS

DR. JERRY M. SHUCK (Cleveland, Ohio): This presentation from the University of Virginia lends itself to comparison to other such surveys of mammographically discovered nonpalpable breast lesions.

Last month at the Western Surgical Association, we presented our experience with 1144 needle localization biopsies. We found an incidence of 25% malignancy rate, compared to this recently presented paper, in which the incidence was 18%. The authors noted that they have found that as well, and they think it will decrease for the rest of us.

If we are becoming more discriminating in whom we biopsy, why should that rate decrease? Our series showed that 75% of the cancers were invasive and 25% were *in situ*. This is similar to most studies.

Could explain why you only had a 33% incidence of invasive cancer versus 75% in most of the other series. Are we all talking about the same lesions? Do we have the same criteria?

You suggest that adjuvant therapy is not necessary even though the follow-up is short. Despite the fact that I really want to agree with that, do your data support that conclusion?

The correlation of pathologic findings with the x-rays may help plan