Prognosis in Stage II ($T_1N_1M_0$) Breast Cancer

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As part of a detailed study of prognostic factors in breast cancer, we have analyzed the ten year survival rates of 524 patients with primary invasive carcinomas 2.0 cm or less in diameter (T_1). This report describes the subset of 142 patients (27%) who had metastases only in axillary lymph nodes ($T_1N_1M_0$). All the patients were treated initially by at least a modified radical mastectomy. Factors associated with a significantly poorer prognosis were: axillary lymph node metastases suspected on clinical examination; perimenopausal menstrual status at diagnosis; tumor larger than 1.0 cm; prominent lymphoid reaction; infiltrating duct or lobular rather than medullary, colloid and tubular carcinoma; and blood vessel invasion. When compared with those patients with negative nodes ($T_1N_0M_0$), the patients with one or more lymph node metastases had a significantly poorer prognosis. Generally, survival rates tended to diminish as the number of involved lymph nodes increased. In this respect, comparison of patients with one–three and four or more nodal metastases provided a significant discrimination of prognostic groups in the entire series. However, for patients with disease limited to Level I, the same discrimination was obtained comparing those with one–two and three or more positive nodes. In the subset with a single lymph node metastasis, the size of the metastasis (micro or ≤2 mm vs macro or >2 mm) was not significantly related to prognosis. Lymph node metastases were significantly less frequent among tumors smaller than 1 cm and special tumor types (medullary, colloid, lobular and tubular). However, no factor proved to be a reliable predictor of the presence of axillary metastases for the single largest group consisting of patients with infiltrating duct carcinoma 1–2 cm in diameter.

PROGNOSIS IN BREAST CANCER is directly related to tumor size and nodal status. Data from several sources indicate a steady improvement, during recent decades, in stage at diagnosis, characterized by a decrease in tumor size and in the frequency of axillary lymph node metastases.[1-3]

In order to better define other prognostic factors, the authors recently undertook a detailed analysis of patients with T_1 (tumor 2 cm or less) breast carcinoma. Among those without apparent metastases at diagnosis ($T_1N_0M_0$), 16% died of breast carcinoma.[4] Of considerable interest was the finding that 27% of T_1 patients had axillary lymph node metastases (N_1). The present report details the authors' findings in $T_1N_1M_0$ patients.

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Materials and Methods

The pathology records of Memorial Hospital for the years 1964 to 1969 were reviewed to identify patients with primary, unilateral invasive breast carcinoma treated by modified or radical mastectomy. A detailed description of the pathology and clinical review procedures and of the data analysis was given in an earlier report.[4] In the present series, data on the number and size of lymph node metastases were also recorded. Among 524 patients with a primary invasive carcinoma 2 cm or less in diameter (T_1), axillary lymph node metastases were found in 142 (27%) cases, the subject of this report.

For preliminary analysis, the 142 patients were divided into two groups, on the basis of the number of lymph nodes involved. Patients with a single lymph node metastases were designated "C" while those with two or more axillary lymph node metastases were classified as "D". There were 61 patients in Group C and 81 in Group D. Because few significant differences were found between Groups C and D most data are presented for the combined series except when important differences were noticed.

Results

Follow-up

The median follow-up period for Groups C and D was ten years. Analysis of survival rates (Fig. 1) revealed no significant difference between Groups C and D. Patients with even single lymph node metastases had

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a significantly poorer prognosis than those with negative lymph nodes.

A detailed summary of final patient status is presented in Table 1. Overall, 51 patients (35%) were found to have had a recurrence attributable to the breast cancer initially treated. Thirty-seven patients (26%) died as a result of their recurrence, an additional nine (6%) were receiving treatment for metastatic disease and four (3%) with systemic metastases died of another illness.

The intervals between initial treatment and recurrence of the disease ranged from less than six months to 11 years. The average interval to disease recurrence was 4.9 years for Group C and 3.9 years for Group D.

Five patients (4%) died of carcinomas other than breast cancer. In Group C, two women died of ovarian carcinoma, three patients in Group D died of carcinoma of the lung, pancreas and colon, respectively.

Age and Menstrual Status at Diagnosis

The patients ranged in age from 27 to 81 years, with a median of 56 years. The frequency of deaths due to carcinoma was appreciably higher among women 51–60 years of age (43%) than in the younger (20%) or older groups (20%). A significantly higher fatality rate was found among perimenopausal women (Table 2).

Preoperative Clinical Findings

Axillary metastases were suspected clinically in nine (14%) of the Group C patients, and in 24 (30%) of those in Group D. As indicated in Table 3, the clinical interpretation of axillary lymph node status was significantly related to the prognosis for the entire group of patients. While a trend was observed in this direction for Group C patients (suspicious adenopathy-recurrence 4/9 (44%); no suspicious adenopathy-recurrence

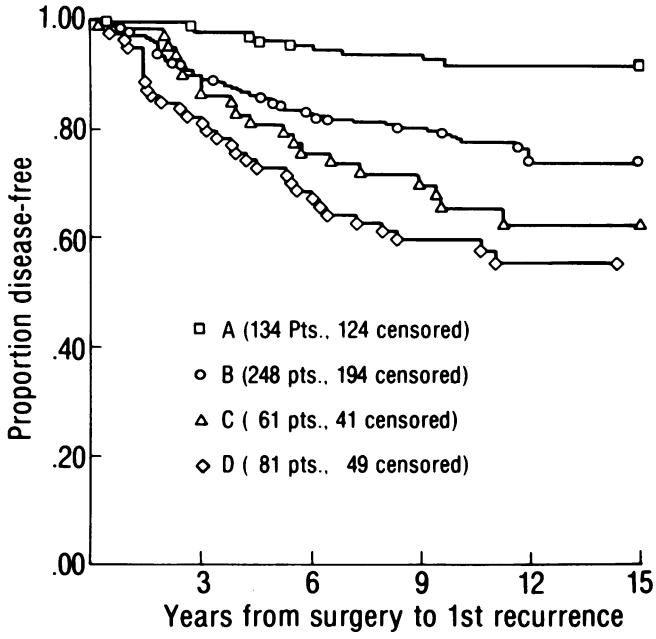

FIG. 1. Graph showing disease-free survival for T_1 patients with negative (groups A [≤1.0 cm] and B [1.1–2.0 cm]) and positive (Groups C and D) axillary lymph nodes.

TABLE 1. *Patient Status at Last Follow-up ($T_1N_1M_0$)*

Status	Patient Group					
	C		D		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Alive, no recurrence	27	43	30	37	57	40
Alive, breast status unknown	0	0	1	1	1	—
Alive, recurrence*	5	9	5	6	10	7
Died breast cancer†	13	21	24	30	37	26
Died other cause with breast cancer‡	2	3	4	5	6	4
Died other cause without breast cancer	11	18	13	16	24	17
Unknown	3	5	4	5	7	5
Totals	61		81		142	

Median follow-up period–ten years. See text for definitions of Groups C and D.

* Group C includes one patient with no apparent disease after treatment of local recurrence and 4 with known systemic recurrence. All Group D patients with recurrence had systemic disease.

† Patients determined to have died of the ipsilateral cancer included in this study.

‡ One patient in Group C and 3 in Group D with known systemic recurrence who died of cardiovascular disease; 1 Group C patient with bilateral cancer for whom laterality of fatal cancer could not be determined; 1 Group D patient determined to have died of contralateral breast cancer.

TABLE 2. *Menopausal Status and Prognosis ($T_1N_1M_0$)*

Survival Status for Groups C and D	Menopausal status					
	Pre-		Peri-		Post-	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Not dead of disease	30	79	12	52	59	78
Dead of disease	8	21	11	48	17	22

$p < 0.04$. Menopausal status not known for five patients.

15/51 (29%)), analysis of the distribution did not reveal a statistically significant difference. However, in Group D there was a significantly greater chance ($p < 0.005$) of recurrence among those with clinically "suspicious" axillary nodes, 13/23 (55%) than among those with clinically negative nodes, 11/57 (19%).

Other clinical parameters evaluated that were not significantly related to prognosis were: clinical features such as skin dimpling, nipple discharge and pain; mammographic interpretation; clinical diagnosis and clinical estimate of tumor size.

Epidemiological Factors

Approximately the same distributions of major epidemiologic variables were seen in Groups C and D. Overall, 9% of the women were single and 91% had been or were married. Thirty per cent were nulliparous. Sixteen patients (11%) had a first degree relative who had been treated for breast cancer, including four (3%) mothers, 11 (7%) with one sister and a single patient who had affected two sisters.

Although not statistically significant, higher recurrence rates were noticed in the following subsets: women who had ever been married, the parous, and those with a first degree relative who had breast cancer. Factors showing no apparent relationship to prognosis were: age at menarche, race, religion, place of birth (foreign or U.S.), history of abortion (spontaneous or induced), cause of menopause (natural or medically induced).

Treatment

The distribution of mastectomy treatment was: standard radical in 80% of the patients; modified radical in 15%; extended radical in 5%. There were no statistically significant differences in recurrence rate and overall survival noticed in relation in these three operative procedures.

A total of 50 (36%) patients received postoperative adjuvant therapy which consisted of local radiation (45 patients), thiotepa (three patients), oophorectomy (one patient) and oophorectomy plus radiation (one patient). Generally, these were patients with multiple lymph node metastases. Adjuvant therapy did not have a significant effect on the overall frequency of recurrence (27/82 [33%] without adjuvant therapy had recurrence vs 21/50 [42%] with adjuvant chemotherapy) or survival (22/82 [27%] without adjuvant therapy died of disease vs 14/50 [28%] with adjuvant therapy).

TABLE 3. *Clinical Axillary Status and Prognosis ($T_1N_1M_0$)*

Survival Status for Groups C and D	Clinically "Suspicious" Lymphadenopathy*			
	No		Yes	
	Number	Per Cent	Number	Per Cent
Not dead of disease	87	81	17	52
Dead of disease	21	19	16	48

$p < 0.003$.

* Clinical observation of axillary lymph node status was missing in one patient.

Tumor Size

The invasive carcinomas in this study ranged from 0.3 to 2.0 cm in diameter (median: 1.4 cm), with no appreciable differences in size distribution or medians (C = 1.3 cm; D = 1.5 cm) between Groups C and D. Fifteen per cent of the tumors were 1.0 cm. or less in diameter and 2% were 0.5 cm or less. The frequency of recurrence and of deaths due to breast cancer tended to increase with tumor size for the entire series (Fig. 2). Similar trends in recurrence and survival rates were observed separately in Groups C and D.

Location of Tumor

The primary tumor involved the left breast more often than the right in the entire series (51%), and this was also seen in Group D separately (57%). However, in Group C, the right breast was more often involved (58%). No appreciable differences were found in the distribution of primary site by quadrant. Laterality and quadrant were not significantly related to prognosis.

Pathological Features of Primary Tumor

Tumor type. Most tumors (90%) were invasive duct carcinomas (Table 4). No deaths due to breast carcinoma occurred among those patients with special tumor types (medullary, colloid, tubular). There were no sig-

nificant differences in the frequency of disease recurrence and death between patients with duct and lobular carcinoma.

Intensity of lymphoid infiltrate. Recurrences and deaths due to breast cancer were significantly ($p < 0.003$) more frequent among women with a tumor that featured a marked lymphoid infiltrate (Table 5). This pattern was seen in a separate analysis of Group C patients, and a similar trend was evident in Group D. In virtually every patient, lymphocytes were more numerous than plasma cells so that analysis of prognosis with respect to the relative proportions of these cells was not possible.

Blood vessel invasion (BVI). Tumor invasion of blood vessels was looked for in sections stained for elastic tissue. Generally, one slide per patient was available. Blood vessel invasion was considered present when tumor cells were found within the lumen of an artery or vein. To be accepted as such, the adjacent corresponding artery or vein had to be evident in the same section. Overall, 16% of the patients had tumor invasion of a blood vessel, and the frequency of this finding did not vary appreciably between Groups C and D. The trend toward increasing fatality with BVI in Groups C and D was significant ($p < 0.03$) for the combined series (Table 6).

Multicentricity. Overall, 23% of mastectomy specimens were found to have carcinoma outside the primary quadrant (multicentricity). In 16%, this was noninvasive, while 7% had separate foci of invasive cancer. No important differences were found between Groups C and D with respect to the frequency and type of multicentricity nor did this factor have an influence on prognosis.

Other pathology variables. No appreciable differences were found between Groups C and D with respect to the following variables: nuclear grade, histologic grade, gross cystic disease, lymphatic tumor emboli, and tumor margin. They were not significantly related to prognosis.

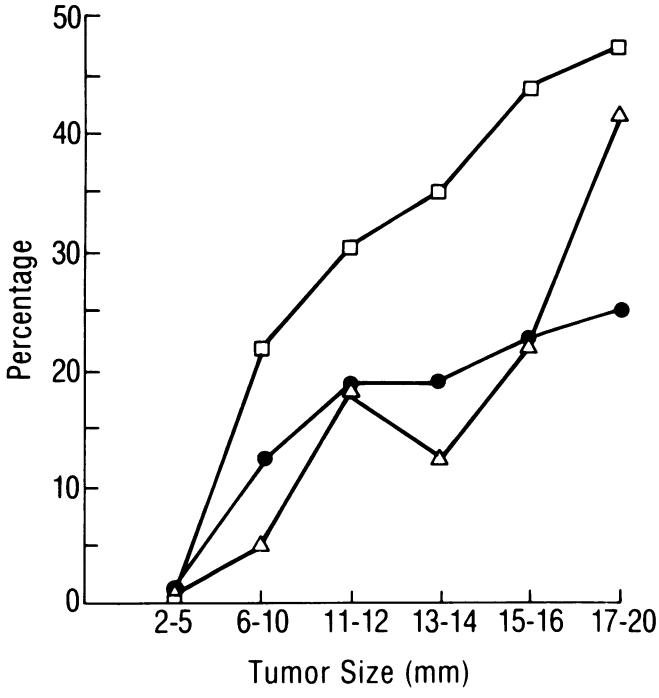

FIG. 2. Relationship of primary tumor size to recurrence and survival among $T_1N_1M_0$ patients. ●: size (142). △: deaths (37). □: recurrence (52).

Bilaterality of Breast Carcinoma

Five patients had concurrent *in situ* carcinoma of the opposite breast (4.0%) and were treated by bilateral mastectomy. One woman (1%) had a prior contralateral mastectomy for *in situ* carcinoma, and eight (6%) developed subsequent contralateral cancer known to be invasive in seven cases. In one patient, death was attributable to a larger contralateral carcinoma with more extensive axillary metastases. In another patient the stage of disease and histologic type were identical for both breasts so that laterality of the fatal cancer was not identifiable.

Contralateral breast biopsy specimens were obtained from 39 other patients at the time of initial treatment

TABLE 4. *Distribution of Tumor Type ($T_1N_1M_0$)*

Histologic Type of Tumor	Survival Status					
	Not DOD		DOD		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Micro invasive duct	1	100	0		1	1
Invasive duct*	93	72	35	28	128	90
Invasive lobular†	4	67	2	33	6	4
Medullary	3	100	0		3	2
Colloid	2	100	0		2	1.5
Tubular	2	100	0		2	1.5

* vs. † = N.S. DOD = dead of disease.

TABLE 5. *Intensity of Lymphoid Infiltrate and Prognosis ($T_1N_1M_0$)*

	Lymphoid Infiltrate			
	Slight		Marked	
Survival	Number	Per Cent	Number	Per Cent
Not dead of disease	87	81	18	53
Dead of disease	21	19	16	47
Totals	108	76	34	24

$p < 0.003$.

Slight: scattered and small aggregates of lymphocytes and plasma cells.

Marked: numerous diffuse and extensive infiltrates of lymphocytes and plasma cells, frequently with follicle formation.

(27% of total). Eight per cent of the biopsy specimens showed atypia and 19% had no significant abnormalities. Patients with concurrent contralateral invasive carcinomas, regardless of the size of the opposite tumor, were excluded from the entire study population of all T_1 tumors.[4]

Other Primary Malignant Tumors

Seventeen other primary malignant tumors were diagnosed in 15 patients (11%). The most frequent primary sites were colon (five patients), cervix (three patients), ovary (two patients), and thyroid (two patients). Individual instances of primary carcinoma at the following sites were also found: lung, endometrium, melanoma, and pancreas. The effect of these other cancers on the survival rate was described above.

Axillary Lymph Node Metastases

Microscopic examination of the axillary lymph nodes in Group C demonstrated micro metastases (≤2 mm) in 35 patients and macro metastases (>2 mm) in 26 patients. Patients with micro- and macrometastases did not differ significantly with respect to recurrence or survival rates (Fig. 3) at ten years of follow-up, although recurrences tended to occur earlier among those patients with macrometastases. There were too few cases for further comparisons based on size of lymph

TABLE 6. *Vascular Invasion and Prognosis ($T_1N_1M_0$)*

	Blood Vessel Invasion*			
	Identified		Not Identified	
Survival Status	Number	Per Cent	Number	Per Cent
Not dead of disease	12	52	91	78
Dead of disease	11	48	26	22
Totals	23	16	117	84

$p < 0.03$.

* Tissue blocks were available to study blood vessel invasion in 140 cases.

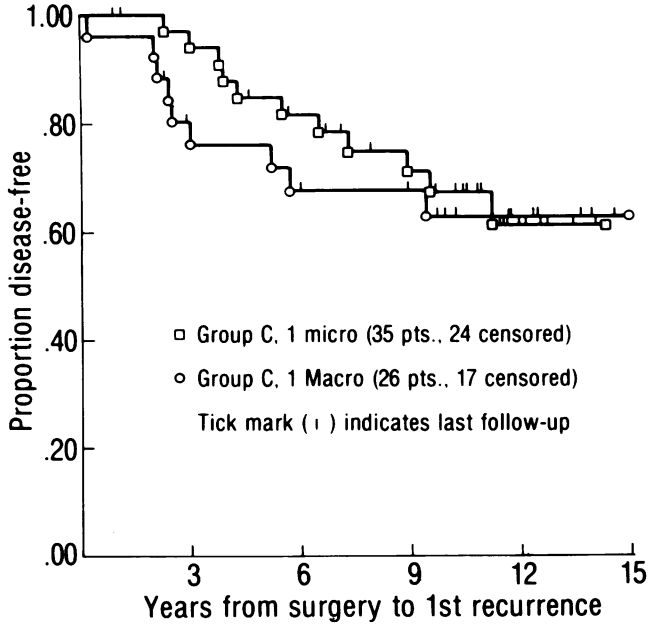

FIG. 3. Graph of disease-free survival for patients with a single positive axillary node, comparing those with a macrometastasis to those with a micrometastasis.

node metastases among patients with multiple lymph nodes involved (*e.g.*, two micro vs two macro).

Lymph node metastases were limited to Level I in 54% of the entire series of 142 patients. Analysis of recurrence related to the number of involved lymph nodes in this group revealed a signficant ($p < 0.04$) trend to earlier recurrence, as the number of involved nodes increased. When patients were grouped as having one–three and four or more axillary nodes involved, those with greater than three nodal metastases had significantly ($p < 0.008$) greater recurrence and fatility rates (Fig. 4). However, final survival did not vary in a consistent manner with the number of lymph node metastases at Level I. Thus, fewer patients with a single lymph node involved survived ten years free of disease than did those with two affected nodes (Fig. 5).

Discussion

Background

A recent comprehensive review of breast cancer in the 1970s reported that "there has been a plateau in the survival curves of breast cancer patients since about 1955."[5] To support this conclusion the authors referred to a paper published in 1975 by Cutler et al.[6] On closer inspection, the data presented by the latter authors offered little support for the conclusion that survival rates in breast cancer had not improved over the last 30 years. In fact, data of Cutler et al. suggested the reverse, since they noticed an upward trend in the five-year survival rates from 53% in 1940–49 to 64% in 1965–69. Their

only reference to the decade of the 1970s was one year survival of 90% for 1970–71, based on the results of the Third National Cancer Survey.

Data obtained at Memorial Hospital reveal a steadily decreasing proportion of patients with lymph node metastases over the past 25 years.[1,7] This has been accompanied by decreasing size of invasive carcinomas and an improvement in survival rates. Others have noticed similar trends.[2,3] The reasons for this apparent change are not clear, and it is likely that a number of factors are involved. It is possible that emphasis on "early detection" is leading to the treatment of more tumors before axillary metastases occur.

Despite this trend to earlier stage and a better prognosis, it is unlikely that there will be dramatic changes in survival rates unless there is a major improvement in the effectiveness of therapy. Until recently, surgery was the dominant primary form of treatment. Improved survival rates with this approach could be achieved only by increasing the proportion of patients with disease limited to the operative field (M_0). One would expect that even if the proportion of M_0 patients increased abruptly by 10%, it would take at least five years to appreciate a resultant improvement in survival rates.

The introduction of systemic adjuvant therapy in patients with axillary metastases offers the prospect that occult distant metastases might be controlled before they become clinically evident. With the risk of systemic spread appreciably increased among women

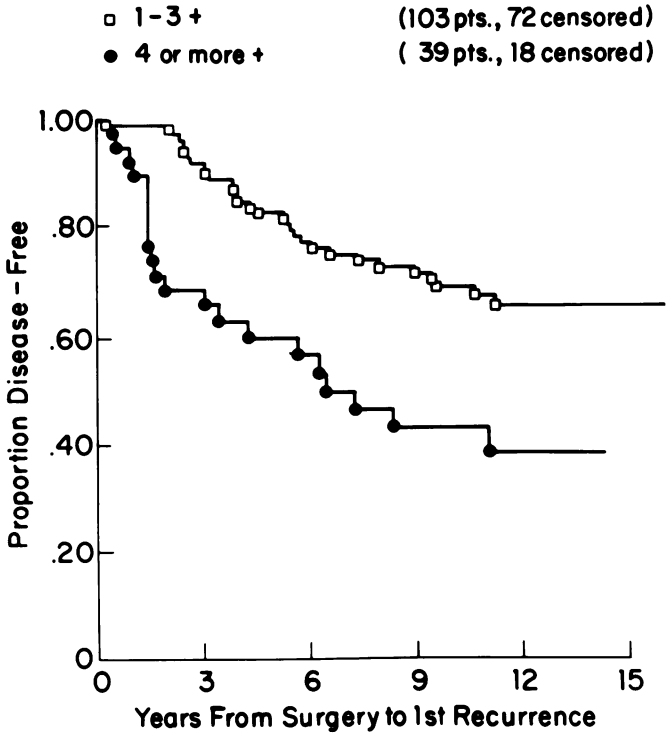

FIG. 4. Graph depicting the effect of number of involved axillary lymph nodes on disease-free survival in $T_1N_1M_0$ patients.

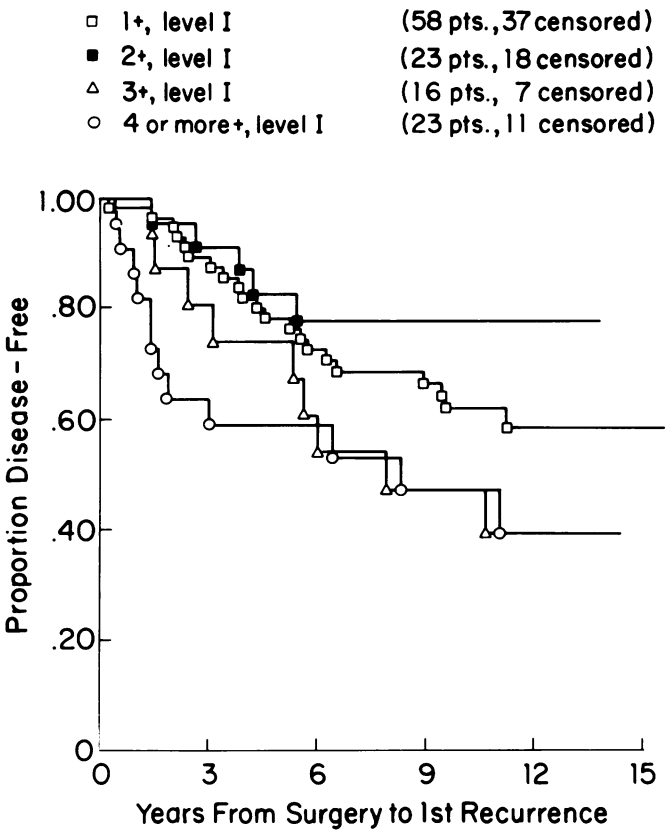

FIG. 5. Detailed analysis of the effect on disease-free survival of number of involved lymph nodes at Level I.

with axillary metastases, the local extent of disease has served as the major indication for systemic adjuvant therapy. Since about one-fourth of the patients with invasive tumors 2 cm or less in diameter have lymph node metastases, a substantial number of women with such relatively small tumors are eligible for this treatment. The present study was undertaken to identify subsets at high or low risk for recurrence among $T_1N_1M_0$ patients.

The observed frequency of lymph node metastases among T_1 patients in the authors' study was somewhat lower than reported in two recently published series. The American College of Surgeons' National Cancer Survey[8] of approximately 24,000 patients with breast cancer described positive axillary nodes in 32% of those with T_1 lesions. This difference may be due to different methods of determining tumor size, since the College Survey was dependent on gross size while our measurements took microscopic extent into consideration. Even more divergent results would be expected from comparisons of studies based on clinical and pathologic staging. Generally, there is a tendency for clinicians to overestimate tumor size, which is most notable for relatively small lesions. One study found clinical classification of tumors as T_1 to agree with pathologic measurements in only 34% of the patients. Among lesions

pathologically measured as T_2, clinical assessment of size was in agreement in 70% of the instances.

A higher proportion (39%) of nodal disease was reported for T_1 patients from Milan, Italy.[9] In this instance, the difference may be due to the fact that only patients treated by radical and extended radical mastectomy were included. Conceivably, patients with "suspicious" axillary findings may have been selected for these procedures.

Survival results also tended to be less favorable in these previously published series. Five-year cure rates in the College Survey for T_1N_0 and T_1N_1 patients were 69 and 46%, respectively. Ten-year survival rates in the Milan series were 90 and 66% for T_1N_0 and T_1N_1 patients.

Comparison with $T_1N_0M_0$ Patients

The ten-year survival characteristics of patients with comparable size breast carcinomas not associated with axillary metastases (T_1N_0) have been previously described.[4] Overall, 16% of the patients experienced a recurrence and 12% died as a result of their cancer. In the present series, limited to T_1 patients proven to have axillary metastases (N_1), the frequencies of recurrence (35%) and death due to breast cancer (26%) were essentially doubled. Since the majority (73%) of T_1 patients did not have axillary metastases, the overall outcome for the entire series of 524 women was 19% recurrence and 15% deaths.

The analysis of negative node patients revealed that the likelihood of recurrence was increased when: a) the tumor was larger than 1.0 cm in diameter; b) there was a prominent lymphoid reaction in a nonmedullary carcinoma; c) the tumor was infiltrating duct or lobular rather than medullary, colloid or tubular; d) when there were intralymphatic tumor emboli within the breast. However, patients with demonstrable tumor invasion of an artery or vein did not have an increased rate of tumor recurrence.

Increasing tumor size and marked lymphoid reaction were associated with a less favorable outcome in the present series, as well. Recurrence was much more likely with duct or lobular carcinomas and not observed in patients with medullary, colloid or tubular carcinoma. While the finding of lymphatic tumor emboli was not indicative of a higher recurrence rate when there were axillary metastases, invasion of arterial or venous channels was more commonly found in tumors from women who developed recurrences after axillary lymph node metastases. Thus, except for different patterns of vascular spread, similar factors were predictive of recurrence in T_1N_0 and T_1N_1 patients.

The primary tumor size had a bearing on the prognosis for patients with positive as well as negative axillary nodes. In the N_1 group, the recurrence rate of 47% for tumors 1.7–2.0 cm was more than twice that found in patients with tumors 0.6–1.0 cm in diameter (22%). There was a trend to increased number of positive nodes with greater tumor size. Thus, the mean size of 61 tumors from patients with a single involved node was 1.3 cm and the same mean size was found in 23 patients with two positive nodes. Larger mean tumor size was associated with 19 patients with three positive lymph nodes (1.6 cm) and 38 having four or more involved lymph nodes (1.5 cm). Comparison of these latter two means revealed that the differences were not statistically significant.

Additional analyses were performed in an attempt to assess the independent influence of tumor size on prognosis after controlling for the number of lymph node metastases. When stratified in 0.4 mm size increments, a positive correlation between size and recurrence was evident only for cases with a single lymph node metastasis among patients with tumors 1.0 cm or larger. There were two few women with two and three positive lymph nodes for reliable interpretation, and in the subset with four or more lymph node metastases only a weak positive trend was found.

Stratification on a broader basis in relation to tumor size was also examined. As shown in Figure 6, analysis of the entire series of patients with tumors 1–2 cm in diameter demonstrated that patients with four or more positive lymph nodes had a significantly poorer prognosis than those with fewer involved nodes.

The seemingly contradictory results obtained for medullary carcinomas and those with a prominent lymphoid reaction underscore the need to define medullary carcinomas accurately.[10] Nonmedullary carcinomas with marked lymphocytic infiltrate tended to be poorly differentiated, to have a low (undifferentiated) nuclear grade and to be at least partly invasive. As noticed previously, these properties were each independently associated with a poor prognosis.[4,11,12] Recently, the authors have also found these to be characteristics of estrogen receptor negative tumors.[13,14] Medullary carcinoma shares many of these features, including estrogen receptor negativety, but differs by being totally circumscribed and having a distinctive syncytical growth pattern.

Given the absence of recurrence from medullary, colloid or tubular carcinomas 2 cm or less in diameter, even when there were lymph node metastases, it may be appropriate to consider these to be low risk patients. At present, it would be difficult to prove that a substantial benefit would accrue to these women from adjuvant therapy even when there are axillary metastases.

Several studies have now shown that blood vessel invasion is generally indicative of a less favorable prognosis, and that this effect is most prominent among patients with lymph node metastases.[15–17] There is some

evidence to suggest that the frequency with which blood vessel invasion is found does not depend on tumor size.[15] However, in the authors' analysis of T_1 patients, those with demonstrable BVI tended to have larger lesions. Among T_1N_0 patients, the difference in mean size was statistically significant (BVI positive 1.35 cm; BVI negative 1.16 cm) and in T_1N_1 patients the same trend, not statistically significant, was observed (BVI positive 1.49 cm; BVI negative 1.38 cm). A substantially larger series of patients would be required to determine the relative importance of tumor size, nodal status and BVI in the setting of T_1 disease.

Analysis of Axillary Lymph Nodes

Clinical assessment of the axillary lymph nodes is correct in about two-thirds of the patients[18,19] with false-positives more frequent than false-negatives when the primary tumor is smaller than 2 cm. Consequently, pathologic examination is necessary for reliable staging. Despite this overall inaccuracy in detecting lymph node metastases, clinical examination proved to be a very significant indicator of prognosis when metastases were thought to be present. Further analysis of our data suggests that this clinical suspicion of metastases was dependent on involvement of multiple lymph nodes. The mean number of lymph nodes with metastases in patients considered to be suspicious was significantly greater than in those not considered to have metastases ($p < 0.05$). Among patients with single lymph node metastases, clinical evaluation of the axilla was not as accurate a predictor of prognosis.

It has become customary to subclassify Stage II patients on the basis of the number of involved lymph nodes. Most often, comparisons are made between patients with one-three and those with four or more involved nodes.[20] This conclusion was recently questioned in a multifactorial two-year follow-up study which found that the prognostic significance of the number of involved lymph nodes varied with menstrual status.[21] The survival rate of women with single lymph node metastases in either menstrual group approached that of patients with negative lymph nodes. Among premenopausal women, the outcome was appreciably worse with two or more involved lymph nodes, while in the postmenopausal group a notable decrease in survival was only seen if there were four or more positive nodes. Others have also questioned the validity of separating patients with more than three positive nodes for treatment stratification.[8]

Our data suggest that separation of patients into groups with one-three and four or more lymph node metastases provides a reasonably useful prognostic discriminator under most circumstances for $T_1N_1M_0$ patients. However, analysis of patients with disease limited to Level I revealed that comparison of women with

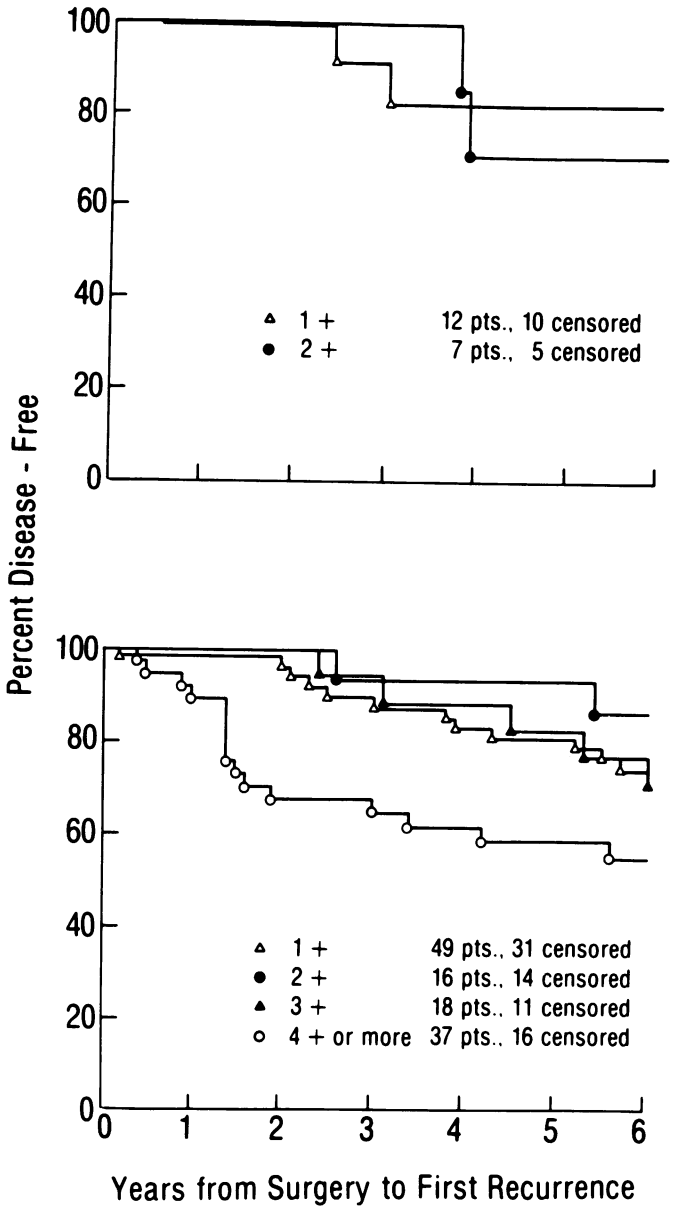

FIG. 6. Graphs depicting disease-free survival related to tumor size and number of axillary lymph node metastases. Upper graph: tumors less than 1.0 cm; lower graph: tumors 1–2 cm.

one to two and three or more proved to be as valuable a discriminant as one to three and four or more. When stratified according to menstrual status, essentially the same trends relating to number of lymph node metastases to prognosis were found for pre- and postmenopausal women (Fig. 7). The authors are, therefore, not able to confirm the variations in prognosis related to menstrual status and number of involved axillary nodes described by others.[21]

In this study, patients with any axillary metastases had poorer prognoses than those with negative lymph nodes. Our results, therefore, differ from several reports which concluded that patients with microscopic metas-

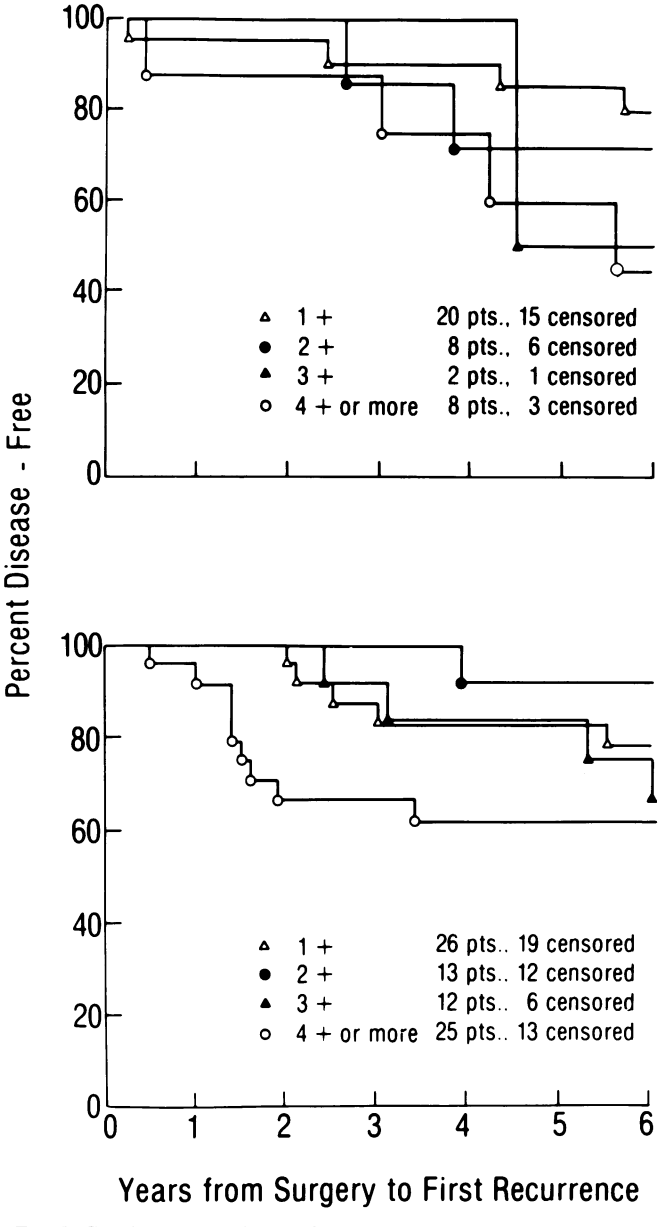

FIG. 7. Graphs showing disease-free survival related to menstrual status at diagnosis and number of axillary lymph node metastases. Upper graph: premenopausal women; lower graph: postmenopausal women. Individual patients with three and four positive nodes respectively were excluded from the upper graph.

tases had a survival rate similar to those of women without demonstrable axillary involvement.[22-24] To some extent, these differences may be the result of variations in study design, since none of the other investigators controlled simultaneously for tumor size, number of involved lymph nodes and level of axillary involvement. Thus, our finding that patients with micro- and macrometastases had similar prognosis must be viewed within the context of the restricted range of tumor size (2 cm or less) that we investigated. It may well be that the significance of these types of metastases will be different for patients with larger tumors. At present, there seems no reasonable basis for excluding $T_1N_1M_0$ patients with micrometastases from adjuvant therapy.

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