Axillary Micro- and Macrometastases in Breast Cancer

Prognostic Significance of Tumor Size

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Recurrence and survival data at 10 years were examined for 147 women with single axillary lymph node metastases found in a modified radical or standard radical mastectomy. The cases were identified through a review of all patients with primary operable breast cancer treated at Memorial Hospital from 1964 to 1970. The patients were stratified into groups according to size of the primary tumor and of the metastatic deposit (micro ≤ 2 mm; macro > 2 mm) as well as level of the positive node. In the entire series, there was a significantly poorer prognosis among those patients with single macrometastases (30/77 patients: 39% recurrence rate) when compared with those having micrometastases (17/70 patients: 24% recurrence rate). A major prognostic difference emerged after stratification by tumor size. Within the first six years of the follow-up period, T_1 patients with negative nodes and those with single micrometasteses had similar survival curves, significantly better than those with macrometastases. However, at 12 years, the survival rate of those patients with either a micro- or macrometastasis was nearly identical, and significantly worse than for those patients with negative lymph nodes. On the other hand, among women with primary tumors 2.1–5.0 cm (T_2), patients with negative lymph nodes or single micrometastases had survival curves that did not differ significantly throughout the course of the follow-up period. Both had an outcome significantly better than observed for patients with macrometastases. These findings have important implications for our understanding of the clinical behaviour of breast cancer and for the stratification of patients entered into randomized treatment trials.

IN THE PAST 20 YEARS, several investigators have correlated the size of axillary lymph node metastases with prognosis in breast carcinoma. Several reports concluded that prognosis was not unfavorably influenced by the presence of micrometastases[1-3] or by minute "occult" metastases detected by serial sectioning of lymph nodes[4-7]. However, none of these studies included sufficient numbers of patients to permit stratification with respect to such variables as primary tumor size, number of involved nodes, level of involvement and size of lymph node metastases. The two largest series consisted, respectively, of 89 patients, each with one or more occult metastases detected by serial lymph node sectioning,[7] and 40 patients with micrometastases of which 14 had had disease limited to level I.[2] With few exceptions, the follow-up period in these studies was less than ten years. In the course on ongoing studies, we have identified a sufficiently large series of patients to permit a detailed stratified analysis of the prognostic significance of single micro- and macrometastases, with a complete follow-up period for at least ten years.

Materials and Methods

The data presented here are derived from a study of patients with primary breast carcinoma treated consecutively at Memorial Sloan-Kettering Cancer Center from 1964 through 1970. Details of the review have been presented elsewhere.[8,9] Follow-up status was ascertained from many sources, including doctors' office records, hospital charts, death certificates and direct inquiries to patients. An opportunity to visit the hospital clinic was offered to patients not recently examined by a physician and this was accepted by about ten patients.

All pathology reports during the seven years under study were examined to identify the following sets of patients: T_1N_0; T_1N_1; T_2N_0; T_2N_1. Histologic sections were then examined by two of the authors to confirm staging as well as for additional pathologic features. A similar pathologic review was performed in any case in which data presented in the original pathology report

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Submitted for publication: April 6, 1981.

0003-4932/81/1100/0585 $00.85

did not permit accurate classification of tumor size or nodal status (N). Hospital charts were reviewed to exclude any patients found to have systemic disease (M) when initially treated. This report is limited to patients who were clinically stage M_0.

The concept of micro- and macrometastases distinguishes between deposits in individual lymph nodes smaller than and larger than 2 mm in diameter. A method of measuring the size of metastases from photocopy images of lymph node sections was described.[1] Others have used an ocular micrometer to determine the largest diameter of metastases.[3] However, there are practical difficulties in both methods due to the fact that metastases in a single lymph node may be found in several, apparently discontinuous deposits. In a substantial number of instances, therefore, these measuring procedures are imprecise and must be regarded only as estimates. In practice, we have found that the microscopic field of view is almost precisely 2 mm across under the following circumstances: using 10× wide-field eye pieces and 10× objective. The estimates obtained with this method correlate closely with measurements using an ocular micrometer.

Statistical significance of differences in proportions was assessed by chi square and exact tests. The method of Kaplan and Meier was used in calculating recurrence and survival curves. The log rank test was used to examine the statistical significance of observed differences. An observation was considered to be statistically significant if $p < 0.05$.

Results

The data presented here deal with two subsets totalling 147 patients ($T_1N_1M_0$ and $T_2N_1M_0$) with metastatic breast carcinoma limited to a single axillary lymph node. In most cases, the involved node was found at level I (axillary nodes lateral to pectoralis major muscle). Data were stratified to compare a micro- with a macrometastasis. All patients had modified or standard radical mastectomies.

$T_1N_1M_0$

The mean number of lymph nodes found in axillary dissections from patients with a micro (18 nodes) or macro (18 nodes) metastasis were not statistically significant. Primary tumors associated with a micrometastasis tended to be smaller (1.3 cm) than those related to a macrometastasis (1.4 cm) but the difference was not statistically significant.

Results for 73 patients with a primary tumor 2 cm or less in diameter are presented in Table 1. No significant differences were found after ten years with respect to survival rates or the frequency of recurrence between patients with single micro- and macrometastases, and this is reflected in nearly identical survival curves (Fig. 1). Essentially the same results were found for the majority of women with metastases limited to level I lymph nodes.

The relationships between patients with and without lymph node metastases are displayed in Figure 2. Within the first three years, women with single macrometastases developed a clear trend to more frequent recurrence than those with micrometastases or no metastases, although the differences were not statistically significant. Separation of the survival curves for negative lymph node patients and those with a micrometastases became evident after six years. Finally, after ten years of follow-up, the prognoses for women with a single micro- or macrometastasis were nearly identical and poorer than for women with negative lymph nodes ($p = 0.01$).

An important influence of tumor size is also evident in Table 1. In the $T_1N_1M_0$ series, there were 16 patients with a primary tumor 1.0 cm or less in diameter with single lymph node metastases. None of nine patients

TABLE 1. *Ten-year Follow-up Results in $T_1N_1M_0$ Patients with Single Lymph Node Metastases*

Patient Group (No. Patients)	NED or DOC		AWD		DOD	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Tumor 2.0 cm or less (73)						
micro (41)	29	(71)	3	(7)	9	(22)
macro (32)	21	(66)	2	(6)	9	(28)
Tumor 1.0 cm or less (16)						
micro (9)	9	(100)	0	(0)	0	(0)
macro (7)	4	(57)	0	(0)	3	(43)
Tumor 1.1-2.0 cm (57)						
micro (32)	20	(63)	3	(9)	9	(28)
macro (25)	17	(68)	2	(8)	6	(24)

NED: Alive, no evidence of recurrence.
DOC: Died, cause other than breast cancer.
AWD: Alive with recurrent breast cancer.
DOD: Died of breast cancer.
Numbers in parentheses indicate per cent.

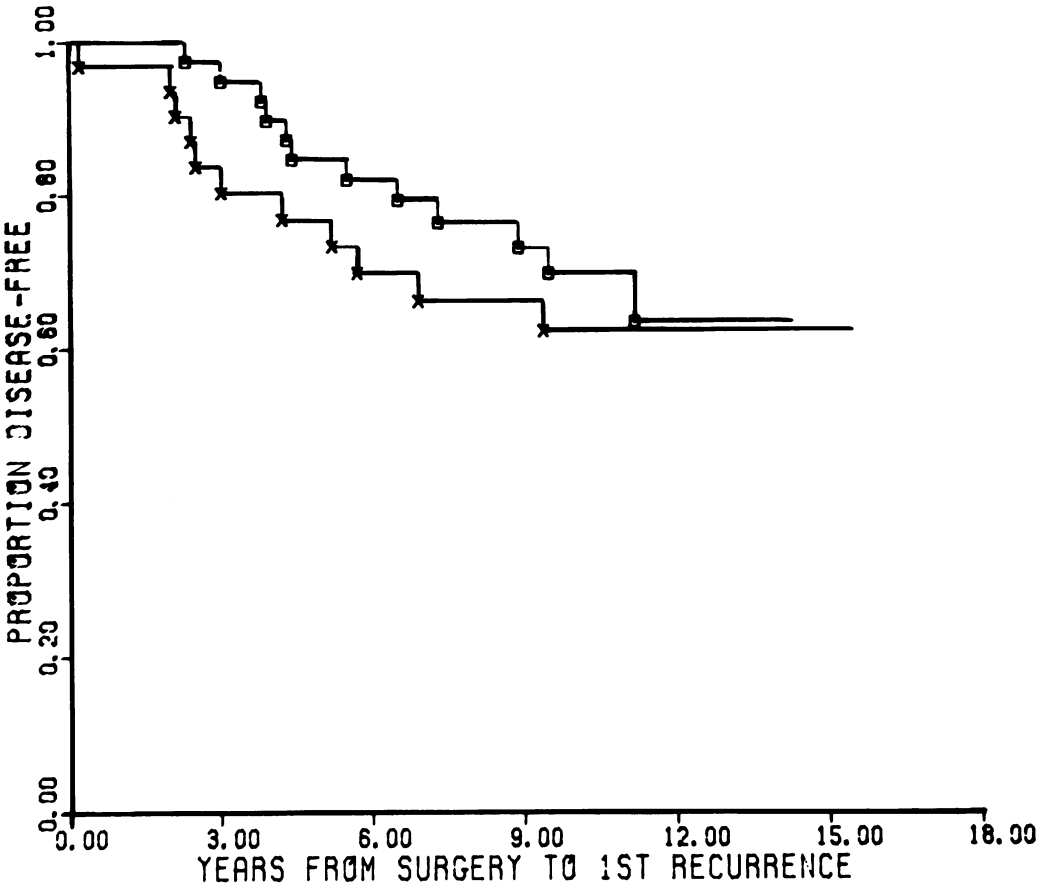

FIG. 1. Disease-free survival curves for T_1N_1 patients with a metastasis in a single axillary lymph node. □:micrometastasis—41 patients. ×: macrometastasis—32 patients.

with micrometastases had recurrent disease. Three of seven patients with a macrometastasis died of breast carcinoma. The subset of $T_1N_1M_0$ patients with a primary tumor 1.1–2.0 cm presented a somewhat different picture. Recurrence and/or death due to breast carcinoma was found in 12 or 32 (38%) women with single micrometastases and in eight of 25 (32%) with macrometastases. Disease recurrence was more frequent in patients with larger primary tumors. In the 1.0 cm or less category, the number of cases is too small for conclusive interpretation, and in the 1.1–2.0 group, no significant difference between those with macro- and micrometastases was found.

The majority (89%) of women with T_1 tumors and a single lymph node metastases had infiltrating duct carcinoma. Included among these 65 patients are two patients having only microscopic foci of invasion associated with gross intraductal carcinoma. Each of these latter patients had a macrometastasis. Except for individual patients who had axillary micrometastases from infiltrating lobular and atypical medullary carcinomas, respectively, all deaths due to disease resulted from duct carcinoma. There was no significant effect of lymphatic tumor emboli in the breast on survival in relation to the presence of micro- or macrometastases.

$T_2N_1M_0$

Seventy-four women with single lymph node metastases had primary tumors 2.1–5.0 cm in diameter. The mean number of lymph nodes in the axillary dissection of patients with micrometastases (20 nodes) was not significantly different from the number isolated from the axillary contents of women with macrometastases (18 nodes). There was no significant difference in tumor size (micrometastasis 3.0 cm; macrometastasis 3.2 cm).

Data describing recurrence and survival rates in Table 2 indicate a significantly less favorable outcome for all patients with single macrometastases when contrasted to all patients with micrometastases ($p = 0.04$). Relevant survival curves in Figure 3 support this conclusion ($p = 0.02$).

Survival curves of T_2 patients with negative lymph nodes and those with a single lymph node metastasis are compared in Figure 4. The recurrence curve for N_0 patients fell between that of women with a micro- and a macrometastasis. Statistical analysis revealed that the following survival curves were significantly different: one micro versus one macro ($p = 0.02$ at five and at ten years); at level I, one micro versus one macro ($p = 0.03$ at five years and $p = 0.06$ at ten years); neg-

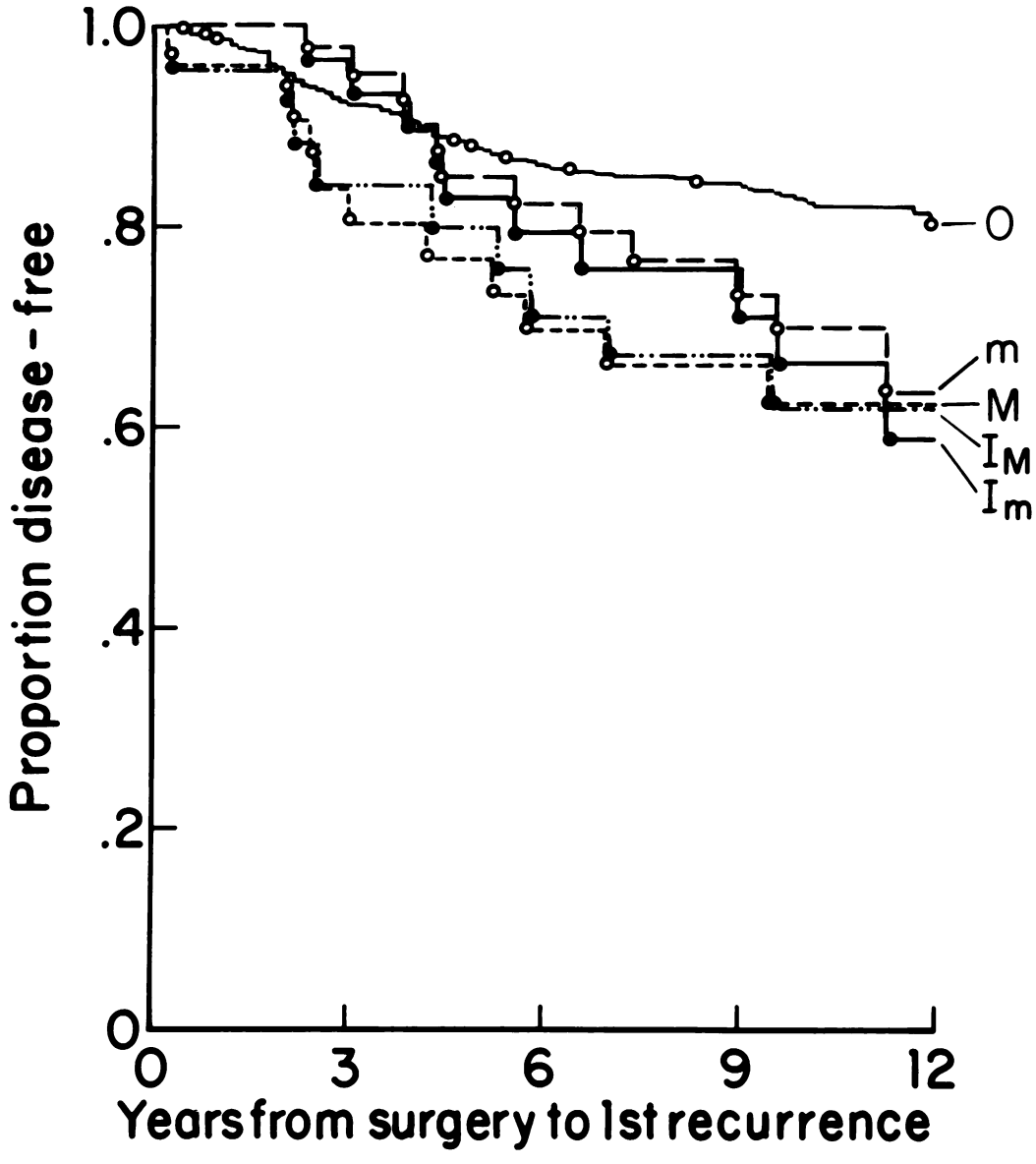

FIG. 2. Disease-free survival curves for T_1N_0 and T_1N_1 (single positive node) patients. O O——O: T_1N_0 (negative lymph nodes)—471 patients. m——: T_1N_1 (one micrometastasis)—41 patients. M - - -: T_1N_1 (one macrometastasis)—32 patients. I_M---·--: T_1N_1 (one macrometastasis at level I)—26 patients. I_m ●——●: T_1N_1 (one micrometastasis at level I)—31 patients.

ative nodes versus one micro versus one macro ($p = 0.02$ and five years and $p = 0.05$ at ten years); negative nodes versus one macro ($p = 0.03$ at five years and $p = 0.07$ at ten years). No significant differences were found at five or at ten years in comparing the curves for negative lymph nodes and single micrometastases.

Table 2 also presents the findings stratified for tumor size. Most tumors (68%) fell in the 2.1–3.0 cm range, and, in this group, the relative frequency of recurrence and death due to breast cancer was virtually identical to the result for the entire group of 74 patients. Analysis of the statistical significance of the distribution in the 2.1–3.0 cm subset yielded a probability value of 0.06. Patients in the other groups with tumors 3.1–4.0 cm and 4.1–5.0 cm also exhibited a trend to more frequent disease recurrence following macrometastases, but the differences did not approach statistical significance.

All but six of the patients had infiltrating duct carcinomas. Among those patients with other tumor types, the two who died of breast cancer each had macrometastases associated with a medullary and atypical medullary carcinoma, respectively. The presence or absence of lymphatic tumor emboli in the breast did not influence prognosis significantly in relation to the presence of single micrometastases or macrometastases (Table 3).

Discussion

An analysis of 142 patients with Stage II ($T_1N_1M_0$) breast carcinoma treated at Memorial Hospital between

TABLE 2. *Ten-year Follow-up Results in $T_2N_1M_0$ Patients with Single Lymph Node Metastases*

Patient Group (No. Patients)	Status					
	NED or DOC		AWD		DOD	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Tumor 2.1-5.0 cm (74)						
micro (29)	24	(83)	1	(3)	4	(14)
macro (45)	26	(58)	2	(4)	17	(38)
Tumor 2.1-3.0 cm (50)						
micro (23)	19	(83)	0	(0)	4	(17)
macro (27)	15	(56)	1	(4)	11	(41)
Tumor 3.1-4.0 cm (19)						
micro (4)	3	(75)	1	(25)	0	(0)
macro (15)	9	(60)	1	(7)	5	(33)
Tumor 4.1-5.0 cm (5)						
micro (2)	2	(100)	0	(0)	0	(0)
macro (3)	2	(67)	0	(0)	1	(33)

Numbers in parentheses indicate per cent.

1964 and 1969 was recently completed.[9] Included in this series were 61 women who were each treated by modified or radical mastectomy with metastatic disease limited to a single axillary node. Analysis of the survival rate with respect to the size of the metastatic deposit (micro or < 2 mm vs macro or > 2 mm) did not reveal a significant difference in prognosis. Because others[1-3] had reported significant differences in survival rates in patients not stratified by tumor size with less than a ten year follow-up study, the authors sought to extend the

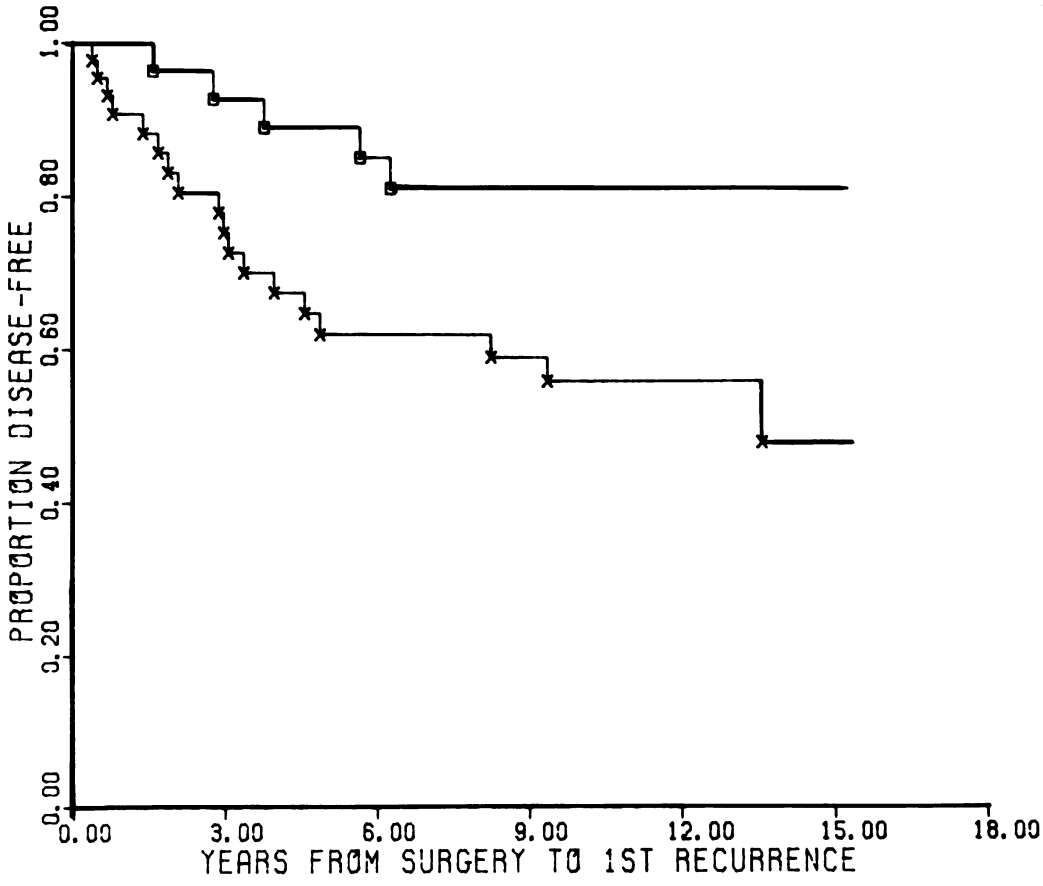

FIG. 3. Disease-free survival curves for T_2N_1 patients with a metastasis in a single axillary lymph node. □: micrometastasis—29 patients. ×: macrometastasis—44 patients.

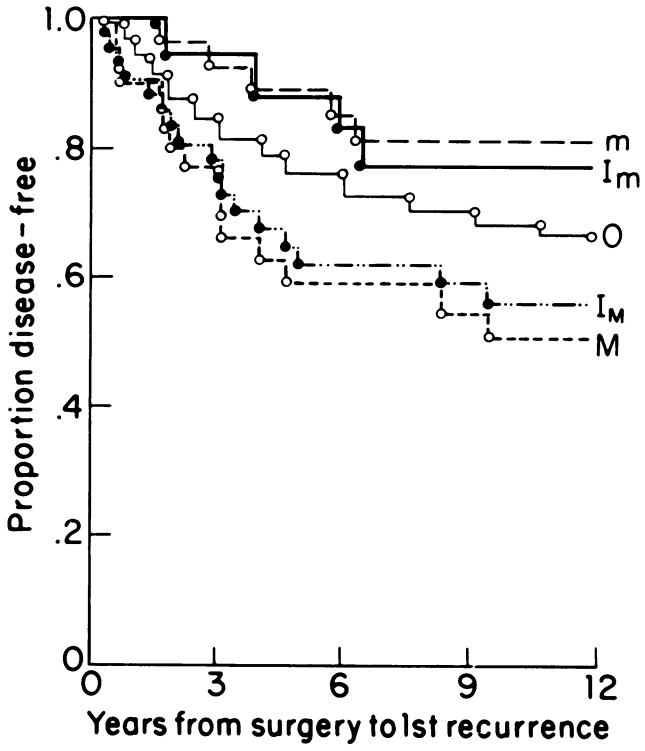

FIG. 4. Disease-free survival curves for T_2N_0 and T_2N_1 (single positive node) patients. O O —— O: T_2N_0 (negative lymph nodes)—282 patients. m——: T_2N_1 (one micrometastasis)—29 patients. M - - -: T_2N_1 (one macrometastasis)—44 patients. I_M---·--: T_2N_1 (one macrometastasis at level I)—34 patients. I_m ● —— ●: T_2N_1 (one micrometastasis at level I)—21 patients.

analysis to patients with T_2 lesions (2.1-5.0 cm) and to expand the study groups by including patients treated in 1970 who were eligible for ten year follow-up examinations.

The earlier study of $T_1N_1M_0$ patients also included 81 women with two or more involved lymph nodes. On reviewing data from that series it was found that the stratification of patients according to tumor size, level of metastases, and number and size of metastases resulted in subgroups too small for reliable analysis. For example, among patients with two positive lymph nodes, it was necessary to compare three categories of metastases: two micro; two macro; and one micro, one macro. As additional patients are studied, those with multiple nodal disease can be investigated, but material presently on hand only permits conclusions related to those with a single positive node.

In order to have well defined subsets of patients for analysis, comparisons were limited to women with metastatic tumor identified in a single axillary lymph node obtained from a standard axillary dissection. No serial sectioning of lymph nodes were undertaken, and the slides examined were those originally prepared for diagnostic purposes, consisting of a single seven micron section of each lymph node. The distinction between finding a macro or micrometastasis did not seem to have been influenced by gross tumor size, nor was it related to the mean number of lymph nodes examined.

Prior studies did not take tumor size into consideration, and concluded that prognosis was less favorable for patients with macrometastases than for those with negative nodes or micrometastases, regardless of the tumor size or the number of involved lymph nodes or the length of the follow-up period. It is clear from the data obtained in this investigation that stratification according to tumor size provides important information regarding the prognostic significance of a single axillary metastasis. These distinctions will, no doubt, prove to be of some importance in the stratification of patients entered in clinical trials, and have a bearing on the choice of adjuvant treatment for individual patients.

It is necessary to emphasize several aspects of the present study which are important differences from prior reports. Several thousand breast cancer patients consecutively treated in a single institution over a seven-year period were reviewed to identify the study population. Histologic sections were examined for each case included in the study, and follow-up information after

TABLE 3. *$T_2N_1M_0$ Prognostic Relationship of Lymphatic Tumor Emboli and Size of Lymph Node Metastasis*

Lymphatic Tumor Emboli (LI) Status	NED or DOC		DOD		AWD	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Micro						
LI + (9)	7	(78)	2	(22)	0	(0)
LI − (20)	17	(85)	2	(10)	1	(5)
Macro						
LI + (7)	3	(43)	3	(43)	1	(14)
LI − (38)	23	(60)	14	(37)	1	(3)

LI +: Lymphatic tumor emboli found in breast.
LI −: Lymphatic tumor emboli not found in breast.
Numbers in parentheses indicate per cent.

10 years was obtained. As a result, two new observations emerged. The patient population was sufficiently large to permit stratification with respect to size of tumor, leading to the finding that micro- and a macrometastases have different relationships to prognosis in patients with T_1 and T_2 tumors. In addition, the follow-up period was long enough to reveal a significant difference between women with negative lymph nodes and those with single micrometastases after ten years, where this had not been apparent with less complete follow-up data.

Detailed examination of Tables 1 and 2 and the survival curves in Figures 2 and 4 revealed a lower recurrence rate for patients with T_2 tumors and single micromatastases (17%) than for those with T_1 tumors, also with a micrometastases (29%). Direct comparison of the survival curves indicated that the observed difference was not statistically significant. However, further analysis was pursued to determine whether there might be a difference in the distribution of prognostic variables which would favor a lower recurrence rate in the T_2 group. Comparison of the relative frequency of prognostic factors in the T_1 and T_2 micro groups revealed significantly higher proportions of circumscribed and low grade tumors in the T_2 group. These prognostically favorable factors might have contributed to a slightly better survival rate in the T_2 micro group, but this could not be documented when a stratified analysis was performed to assess the statistical significance of differences in survival while controlling for the presence of differentiation and circumscribed tumors. It is conceivable that other factors, such as differences in growth rate, influence the prognosis of patients with T_1 or T_2 tumors and single micrometastases.

Experimental studies performed on laboratory animals have led some investigators to propose that dissemination regularly occurs early in the course of human mammary carcinoma. The basis for this conclusion was recently reviewed by Fisher.[10] This hypothesis has profound implications for the clinical management of the disease, leading to greater emphasis on systemic treatment and less extensive local surgical therapy. However, it is only a hypothesis and we know of no data now available which offer convincing proof that it is correct or that it necessarily applies to all patients.

Data obtained in this and other studies clearly indicate that about 80% of the patients with T_1N_0 disease never develop clinical evidence of metastases. The outcome is still quite favorable for those patients with T_1N_1 disease, especially when axillary metastasis is limited to a single lymph node. These observations neither prove nor disprove the hypothesis that breast cancer is a systemic disease once it is invasive. They do suggest, however, that even if all tumors did shed cells, this is a clinically significant hazard for some, but clearly not all patients. Consequently, continued emphasis should be placed on the search for epidemiologic, clinical, pathologic and/or biochemical prognostic factors that will permit the identification of patients at high or low risk for recurrence. To the extent that this approach is successful in separating prognostic groups, it would provide a rational basis for the selective use of adjuvant therapy rather than indiscriminant treatment based on the hypothesis that dissemination occurs in all patients with breast cancer.

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