Relation of Tumor Size, Lymph Node Status, and Survival in 24,740 Breast Cancer Cases

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Two of the most important prognostic indicators for breast cancer are tumor size and extent of axillary lymph node involvement. Data on 24,740 cases recorded in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute were used to evaluate the breast cancer survival experience in a representative sample of women from the United States. Actuarial (life table) methods were used to investigate the 5-year relative survival rates in cases with known operative/pathologic axillary lymph node status and primary tumor diameter. Survival rates varied from 45.5% for tumor diameters equal to or greater than 5 cm with positive axillary nodes to 96.3% for tumors less than 2 cm and with no involved nodes. The relation between tumor size and lymph node status was investigated in detail. Tumor diameter and lymph node status were found to act as independent but additive prognostic indicators. As tumor size increased, survival decreased regardless of lymph node status; and as lymph node involvement increased, survival status also decreased regardless of tumor size. A linear relation was found between tumor diameter and the percent of cases with positive lymph node involvement. The results of our analyses suggest that disease progression to distant sites does not occur exclusively *via* the axillary lymph nodes, but rather that lymph node status serves as an indicator of the tumor's ability to spread.

***Cancer* 63:181–187, 1989.**

NUMEROUS STUDIES, done in many countries, have shown the value of using tumor size and nodal status to estimate prognosis in breast cancer.[1–15] These observations are so universally accepted as to form the basis of the TNM staging that is promulgated by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). This staging system uses three variables: diameter of the primary lesion (T), number of lymph nodes involved with the metastatic tumor (N), and distant metastatis (T). It is also widely accepted that age, race, histologic type, hormonal receptor status, and a number of other significant variables may influence an individual's prognosis.[16–23]

The relation between tumor size, lymph node status and outcome has been qualitatively known for many years. Fisher *et al.*, in a study of 2578 breast cancer patients, found a relation between size, nodal status and outcome back in 1969. However, these authors concluded that size alone was not as consequential to the patient's survival as were the other factors.[24] Valagussa *et al.* studied 716 patients in 1978 and noted that survival rates were directly proportional to the size of the primary tumor in node positive cases, but not in node-negative patients.[25] These authors were not able to quantitatively relate size with nodal status and survival, owing in part to relatively small sample sizes and in part to the lack of a population based comparison group. No effort was made to relate the number of positive nodes to the number of nodes examined in these earlier studies. In a limited series of patients from the SEER program, Smart and co-workers in 1978 reported a linear relation between tumor size and lymph node involvement.[26]

Since 1973, the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute has collected data on the cancer survival experience of nearly 10% of the general population of the United States. This is accomplished through the maintenance of nine SEER population based registries that cover five states and four metropolitan areas (Connecticut, Hawaii, Iowa, New Mexico, Utah, Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound). Cases in these catchment areas represent a cross-section of cancer cases in the general medical practice. The Seer sample is composed of 85% white and approximately 8% black, with 16% being less than 50 years old, 47% in the 50 to 69 year age range, and 37% being 70 years or older. In 1977, SEER registries began to code tumor size and lymph node status in a form

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Accepted for publication July 11, 1988.

TABLE 1. Study Criteria for Breast Cancer Survival Analysis

	No.
Cases diagnosed between 1977–1982	63,316
Excluded	
Study exclusions*	−11,531
Cases with <8 lymph nodes examined	−18,481
Selected for study	
Pathologic lymph node status and tumor size recorded	24,740

* Study exclusions: male cases, cases with race unknown, carcinomas *in situ*, no microscopic confirmation, distant metastasis at diagnosis, breast cancer is not first primary, and disease information appears only on death certificate.

suitable for our analysis. In this report, we have used the SEER data to analyze the survival experience of over 24,000 women newly diagnosed with breast cancer between 1977 and 1982. We investigated the quantitative relation between size and axillary lymph node status to breast cancer survival in these women who were drawn from a wide range of medical practice.

Case Selection and Methods

Data from the SEER Program of the National Cancer Institute were used in the analysis of breast cancer patient survival. Details of the purposes, functions, and procedures for SEER have been published elsewhere.[27] A total of 63,316 breast cancer cases diagnosed between January 1, 1977 and December 31, 1982 and under active follow-up until December 31, 1983 met our eligibility criteria (Table 1) of microscopicaly confirmed, first primary breast cancer in women. Of these cases, 24,740 had recorded operative/pathologic primary tumor diameter and at least eight lymph nodes examined and were thus selected for extended analysis. Selected cases included tumors recorded as microscopic in size while excluding those reported as diffuse since size was not recorded. Cases that were metastatic at the time of diagnosis were excluded from analysis, as were *in situ* carcinomas, the latter constituted approximately 5% of all cases.

The survival experience of these 24,740 cases was analyzed using the actuarial (life table) method.[28,29] All survival rates reported are cumulative relative rates, obtained by adjusting the observed survival with the expected mortality experience in a general population with the same age and race distribution. Relative rates thus reflect the number of cases that are specifically due to breast cancer as compared to deaths from all other causes. In this report, we converted the 5-year relative survival rates to percentages for ease in interpretation.

Straight lines were fitted to the date using the least squares method of linear regression. For comparisons of slopes we used the General Linear Models (GLM) procedures of Statistical Analysis System (SAS) to test the null hypothesis of homogeneity of slopes.[30]

Results

Overall Characteristics and Survival Experience of Cases

Infiltrating ductal cancers accounted for 83.4% of the cases, with 7.4% lobular and the remaining 9.3% distributed among medullary, mucinous, comedo, tubular, and papillary histologic types. We have reported previously on the survival of this cohort as a function of tumor histologic type.[31] The overall relative 5-year survival rates for the 24,740 cases in our analytic cohort was 81.7%.

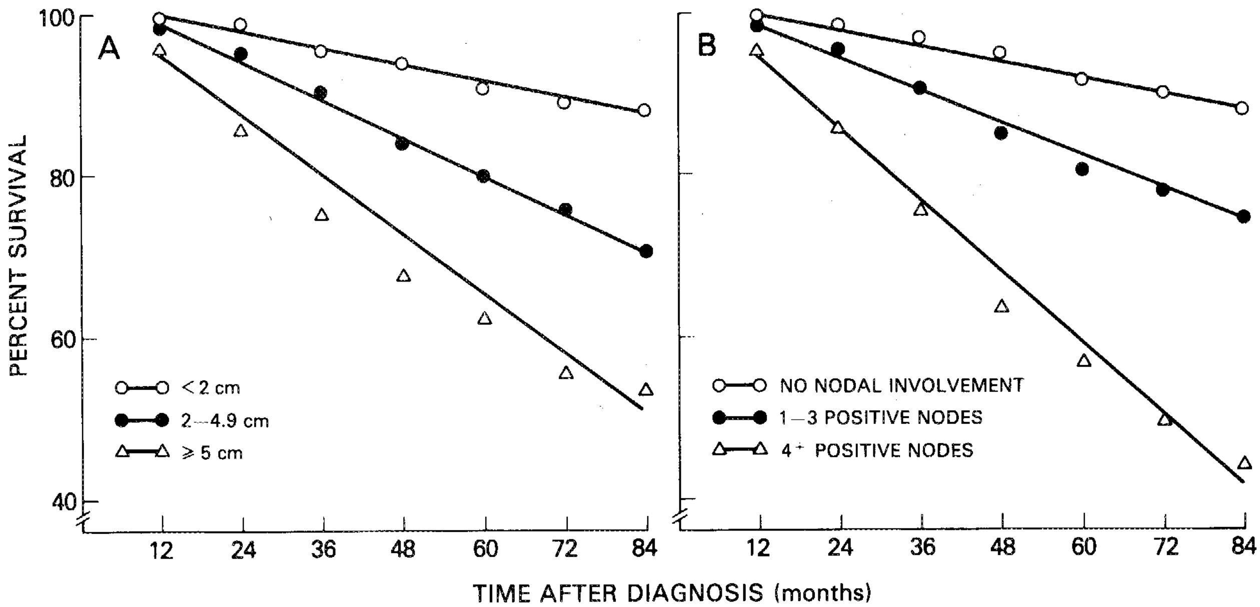
Case distribution by tumor size and lymph node status is summarized in Table 2. We notice that 57.6% of all tumors in the sample were between 1.0 and 2.9 cm in diameter and that 54.4% of all cases had lymph nodes negative for metastatic tumor at the time of surgery.

Effect of Tumor Size and Axillary Lymph Node Status on Survival

Figures 1A and 1B illustrate the effect of tumor size and lymph node status on 5-year survival. As expected,

TABLE 2. Distribution of Breast Cancer Cases by Size and Lymph Node Status

Diameter (cm)	Selected cases		Lymph node status: Negative nodes		1–3 Positive nodes		4+ Positive nodes	
	No.	(Percent)	No.	(Percent)	No.	(Percent)	No.	(Percent)
<0.5	339	(1.4)	269	(79.4)	53	(15.6)	17	(5.0)
0.5–0.9	996	(4.0)	791	(79.4)	140	(14.1)	65	(6.5)
1–1.9	6984	(28.2)	4668	(66.8)	1574	(22.5)	742	(10.6)
2–2.9	7282	(29.4)	4010	(55.1)	1897	(26.1)	1375	(18.9)
3–3.9	4329	(17.5)	2072	(47.9)	1185	(27.4)	1072	(24.8)
4–4.9	2112	(8.5)	845	(40.0)	549	(25.6)	727	(34.4)
>5.0	2698	(10.9)	809	(29.9)	630	(23.4)	1259	(46.7)
Total	24740	(100)	13464	(54.4)	6019	(24.3)	5257	(21.2)



FIGS. 1A AND 1B. Relative survival of breast cancer as a function of (A) primary tumor diameter and (B) axillary lymph node status.

both increased primary tumor diameter and increased lymph node involvement have a negative influence on percent of relative survival. From the figure, it is apparant that cases with four or more positive lymph nodes have the poorest survival experience, regardless of tumor size.

The relation between these two prognostic indicators and their mutual effect on survival is given in Table 3 and shown graphically in Figure 2. As the diameter of the primary tumor increases from less than 2 cm to 5 cm or more, the 5-year survival declines from 96.3% to 82.2% for node-negative cases. The effect of lymph node involvement is shown by the decline in survival within each size category with increased lymph node involvement. For example, for the tumors less than 2 cm, survival decreases from 96.3% for node-negative cases to 87.4% for those with one to three positive axillary nodes, and to 66.0% for cases with four or more positive nodes. For tumors 2 to 4.9 cm in diameter, survival decreases from 89.4% for node negative patients to 79.9% for patients with one to three positive nodes, and to 58.7% for patients with four or more positive nodes. Based on data presented in Figure 2, both tumor size and nodal status appear to have an independent adverse effect on survival.

Figure 3 shows the quantitative relation between size, lymph node status, and survival for cancers ranging in size from less than 0.5 cm in diameter to those equal to or greater than 5.0 cm. The relation between size and survival at 5 years is linear regardless of lymph node status. For node-negative patients, the adverse effects of size on survival is less than that for node-positive patients. For patients with positive nodes, the effect of size on survival is similar whether one to three nodes or four or more nodes are involved. The vertical difference between the lines in Figure 3 represents the adverse effects of nodal status on survival for tumors of the same size. There is a small subset of tumors (those 0.5–0.9 cm, with four or more positive nodes [N = 82, Table 4]) for which the linear relation described between tumor size and survival does not hold.

Probability of Lymph Node Involvement

In Figure 4, the probability of lymph node involvement (defined as the percentage of cases with one or more pos-

TABLE 3. Five-Year Breast Cancer Survival Rates by Tumor Size and Lymph Node Status

Size LN Status	No.	Relative survival (%)
<2.0 cm		
Total	8319	91.3
Negative nodes	5728	96.3
1–3 Pos nodes	1767	87.4
4+ Pos nodes	824	66.0
2–5 cm		
Total	13723	79.8
Negative nodes	6927	89.4
1–3 Pos nodes	3622	79.9
4+ Pos nodes	3174	58.7
>5.0 cm		
Total	2698	62.7
Negative nodes	809	82.2
1–3 Pos nodes	630	73.0
4+ Pos nodes	1259	45.5

LN: lymph node; Pos: positive.

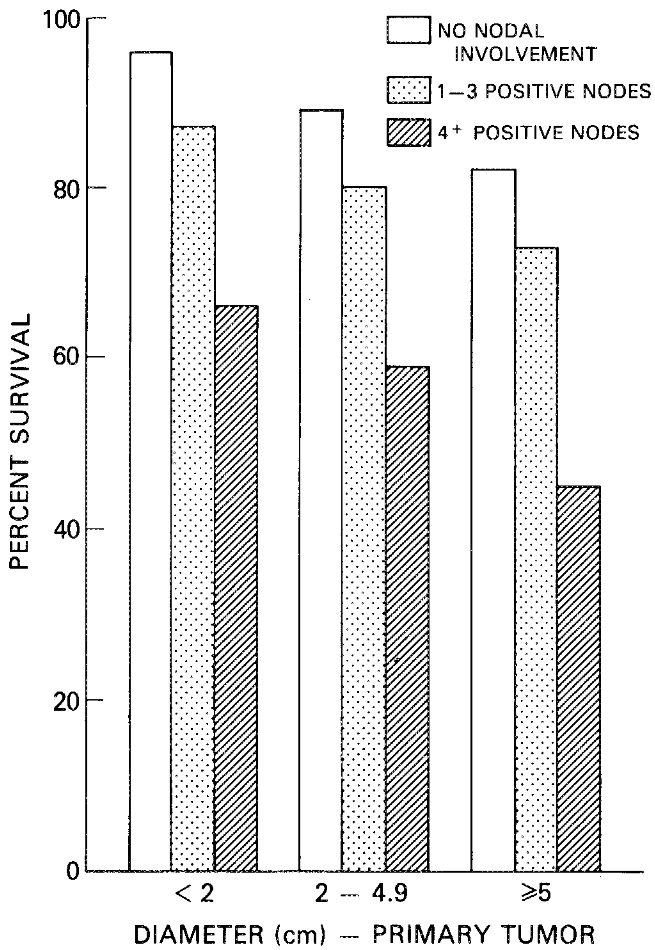


FIG. 2. Five-year relative survival of breast cancer as a function of both tumor diameter and lymph node status.

itive nodes for each size) is plotted against the diameter of the primary tumor. The relation between the tumor diameter and the probability of nodal involvement in all tumor sizes appears linear for the range of tumor sizes shown. For patients with cancers 5 cm or greater, 71.1% are expected to have at least one node involved.

The relation of tumor size to number of lymph nodes involved is shown in Figure 5. In our data, the point at which the two curves for one to three positive nodes *versus* four or more positive nodes intersect (at a tumor size of approximately 3 cm) defines two groups of patients. Among the cancers that are less than 3 cm that have metastasized to axillary nodes, there is a greater probability of the patients having only one to three positive nodes rather than four or more positive nodes. In cancers greater than 3 cm, however, the probability of finding patients with 4 or more positive nodes continues to increase. However, beyond 3 cm, increasing tumor size does not increase the probability of finding cases with one to three positive nodes.

Discussion

Figure 6 summarizes the case distribution by size and lymph node status, and the survival experience of 24,740 women diagnosed with primary breast cancer between January 2, 1977 and December 31, 1982. The markedly poorer survival of women with four or more axillary lymph nodes positive (21% of this cohort) is evident for all tumor sizes. This is especially striking when one contrasts the survival rates for tumors less than 2 cm; those with no positive nodes or only one to three nodes involved have a 77% to 99% relative survival to 5 years, whereas those with four or more positive nodes have a maximum 64% survival.

Since patients from all ages and races were used in this study, the data represent the average over the entire group. Within the group, however, are subsets that have increasing or decreasing survival experiences for the same tumor size and nodal status. An analysis of the effects of age and race on the prognostic indicators investigated in this study will be reported separately.

Our data on the role of tumor size in predicting axillary metastasis confirm and extend the results of surveys by the American College of Surgeons[32,33] which showed that

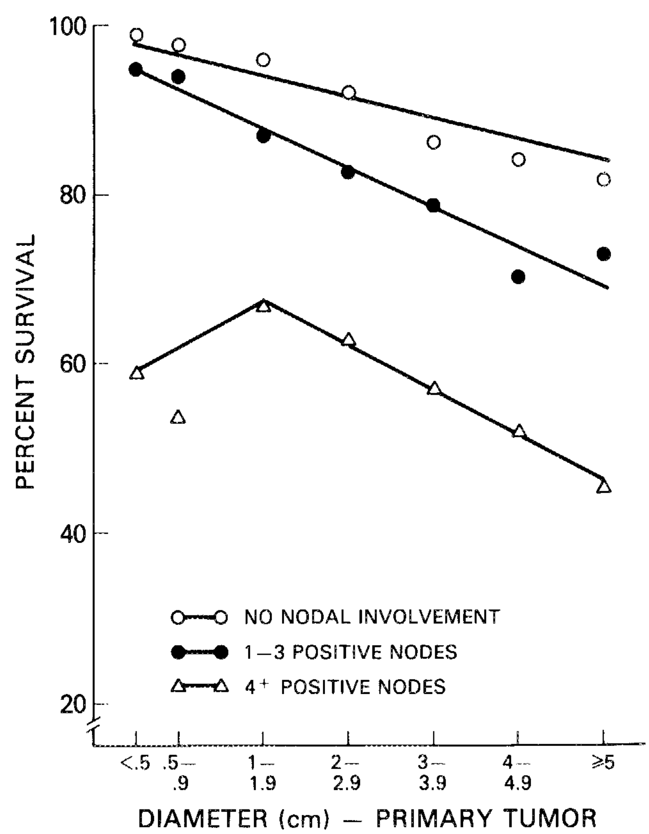


FIG. 3. Relation of tumor diameter and lymph node status to 5-year relative survival. Slopes for one to three (● —— ●) and for four or more (△ —— △) positive nodes are not significantly different ($P < 0.005$).

5-year survival decreased as the tumor size and the probability of axillary metastasis increased. We notice, for example, that even for tumors less than 1 cm, positive nodal status is found in approximately 20% of our cases. This has been reported previously.[34] Moreover, we have shown (Fig. 3) that in both node-negative and node-positive patients, the contribution of tumor size to mortality is a linear function of tumor diameter. The effect of size is greater for node-positive patients than for node-negative patients. This differs from the report by Vallagussa *et al.*[25] who found no relation between survival and tumor size in node-negative women, and Fisher *et al.*[24] who found a direct relation between survival and size only in women with four or more positive nodes.

Our results also indicate that both size and lymph node status are independent prognostic indicators, since survival declines with increasing size when nodal status is held constant, and survival declines when nodal status increases and size is held constant. It seems likely, however, that both nodal status and survival are reflections of the same biological process, *i.e.*, the ability of the tumor to spread either locally or to distant sites. Furthermore, our data show that a consistent relation exists between the variables of tumor size and the probability of nodal metastasis (Fig. 4). Smart *et al.*, in a review of 8587 patients recorded in the SEER program in 1975, showed a linear relation between size of the primary tumor and lymph node involvement.[26] Hence, we suggest that the metastatic potential evolves as the tumor grows, and that nodal status simply reflects the ability of the tumor to spread. However, the evolution of this metastatic potential is not the same in all tumors. Nonetheless, it is this relation between tumor size, nodal status, and survival that makes the TNM staging system work; otherwise there would be no consistent correlation between nodal status, distant metastasis, and prognosis.

We conclude from the data that cancers are more likely to spread directly from the breast to distant sites, with the axillary nodes representing a local site which serves as an indicator for the tendency to metastasize. Clinically, nearly 25% of patients who are node negative at the time of surgery eventually develop distant metastisis. Presumably, in these patients, the tumor has spread by other routes to

TABLE 4. Five-Year Breast Cancer Survival Rates for Seven Tumor Sizes and Three Categories of Lymph Node Involvement

Size LN status	No.	Relative survival (%)
<0.5 cm		
Total	339	96.2
Negative nodes	269	99.2
1–3 Pos nodes	53	95.3
4+ Pos nodes	17	59.0
0.5–0.9 cm		
Total	996	94.9
Negative nodes	791	98.3
1–3 Pos nodes	140	94.0
4+ Pos nodes	65	54.2
1.0–1.9 cm		
Total	6984	90.6
Negative nodes	4668	85.8
1–3 Pos nodes	1574	86.6
4+ Pos nodes	742	67.2
2.0–2.9 cm		
Total	7282	84.3
Negative nodes	4010	92.3
1–3 Pos nodes	1897	83.4
4+ Pos nodes	1375	63.4
3.0–3.9 cm		
Total	4329	77.0
Negative nodes	2072	86.2
1–3 Pos nodes	1185	79.0
4+ Pos nodes	1072	56.9
4.0–4.9 cm		
Total	2112	70.3
Negative nodes	845	84.6
1–3 pos nodes	540	69.8
4+ Pos nodes	727	52.6
>5.0 cm		
Total	2698	62.7
Negative nodes	809	82.2
1–3 Pos nodes	630	73.0
4+ Pos nodes	1259	45.5

LN: lymph node; Pos: positive.

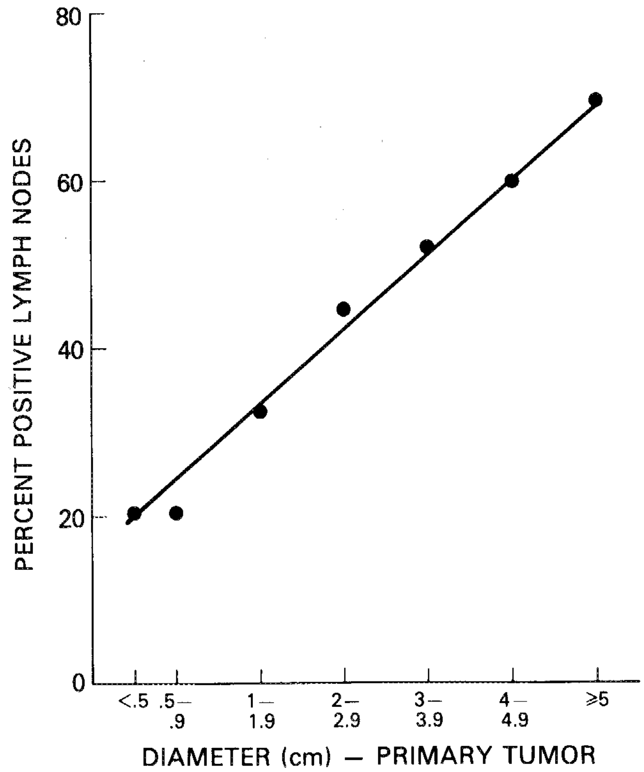


FIG. 4. Percent positive axillary lymph nodes as a function of primary tumor diameter.

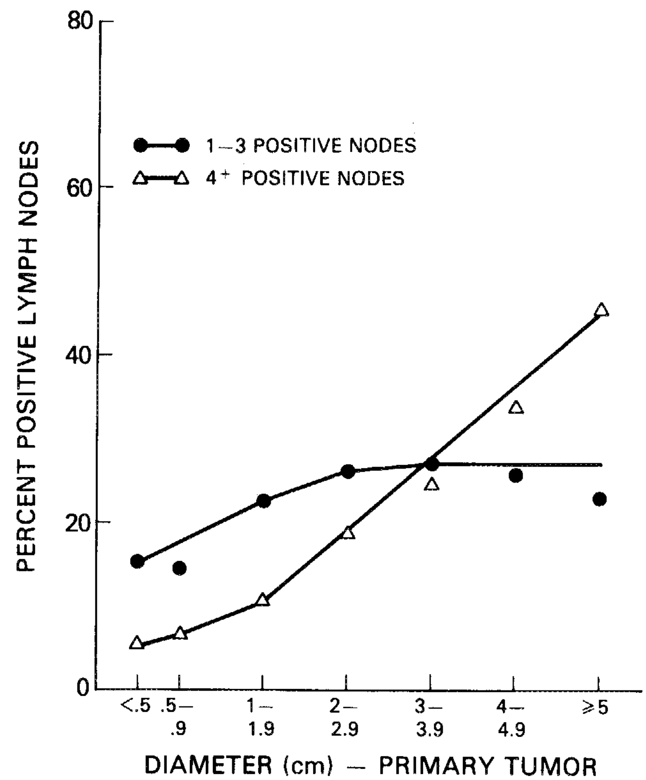


FIG. 5. Relation of tumor diameter to percent involvement of one to three *versus* four or more positive lymph nodes.

distant sites. Regardless of the mechanism of metastasis, nodal status remains the single most important indicator for prognosis.

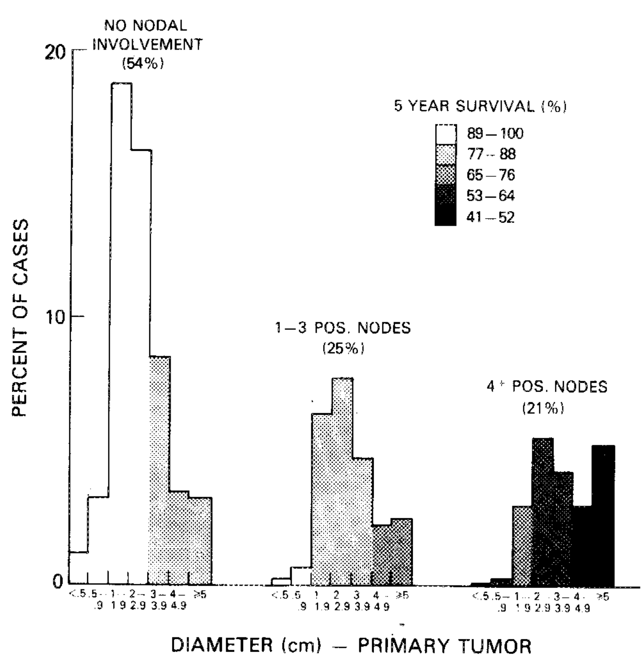


FIG. 6. Distribution of 24,740 breast cancer cases by tumor size and lymph nodes status. Shading indicates 5-year relative survival for each category.

Finally, because of our large sample size, we were able to identify a subset of small but highly virulent tumors that have metastisized to four or more nodes by the time of diagnosis. These cases have a 5-year survival rate of only 54% to 59% compared with a 94% to 95% survival rate seen in patients with the same tumor size, but with only one to three nodes involved. This group (N = 99, Table 5) seems to be an exception to the rule that the metastatic potential evolves as the tumor develops. For this small subset of tumors, the metastatic potential is clearly expressed early in the course of the disease. It would be of interest to compare these small, agressive tumors to the interval cancers found in screening programs.

These results show the benefit of using stage as an effective guide to treatment. For example, our data indicate that patients with cancers 1.0 to 1.9 cm in size with one to three positive nodes have approximately the same 5-year survival experience as patients with much larger cancers (3.0–3.9 cm) and negative nodes.

Our results, based on 24,740 cases drawn from the general medical practice, confirm that the TNM staging system for breast cancer is useful for estimating prognosis. Nonetheless, other prognostic factors exist, such as differentiation and nuclear grade, that also should be considered in individual patient management. Tumor size and nodal status, the basis for the TNM system, are practical parameters for estimating prognosis. As early detection increases the number of smaller tumors found, and as more patients are treated by segmental resection, the assessment of regional lymph nodes will become less important clinically.

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