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Pathologic Identification of Poor Prognosis Stage I ($T_1N_0M_0$) Cancer of the Breast

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Twenty to 40% of Stage I($T_1N_0M_0$) cancers of the breast recur in ten years. This is an attempt to identify those patients in whom the disease is likely to recur. On the basis of a study of the histologic changes in the tumor and treatment failures poor prognosis was associated with several histological characteristics: poor cytologic differentiation; lymphatic permeation; blood vessel invasion and invasion of the tumor into the surrounding soft tissue. This classification was then applied to 363 cancers of the breast seen over a five year period and followed three to eight years. There were 203 Stage I ($T_1N_0M_0$) tumors in the group. Ninety-four of the 203 Stage I tumors had one to four of the above histologic characteristics; 109 had none. Among the 109 patients characterized as good risks there were two treatment failures (2%). In the group of 94 with any high risk histologic features there were 47 treatment failures (50%) which were statistically significant ($p = 0.001$). The histologic changes had a cumulative effect on the degree of malignancy of the tumor. Pathologic changes in the tumor identified those patients whose Stage I ($T_1N_0M_0$) tumors were likely to recur.

THE BEST RESULTS in the treatment of invasive cancer of the breast have been obtained in those patients with lesions smaller than 2 cm in diameter whose cells have not yet spread to the regional lymph nodes ($T_1N_0M_0$). However, the ten year survival of such patients is only 60–80%.[1,3] Identification of the patients whose disease is likely to recur would isolate those who require more or different treatment. This report details identification of this group on the basis of pathologic evaluation of the tumor.

At the time of their original treatment we noted several Stage I ($T_1N_0M_0$) breast cancers in patients whose tumors had histologic characteristics suggestive of high malignant activity. When these patients did poorly over a period of a few years, it was decided to review such cases and correlate the microscopic picture with the long-term course of the patients.

The original pathology reports of all patients who had definitive surgical treatment for primary breast cancer at St. Vincent's Hospital from January 1, 1971 through December 31, 1975 were reviewed. Excluded were bilateral simultaneous breast cancers (3 patients), second primary breast cancers (6 patients) and males (2 patients). There were 363 patients in the group. Among those there were 203 patients whose cancer grossly was less than 2 cm in diameter and had not spread to the axillary lymph nodes on histologic examination ($T_1N_0M_0$). The original pathology reports of these patients were reviewed. Particular attention was directed to age, size of the tumor, presence of disease in lymph nodes, histologic type, degree of differentiation, cell reaction to the tumor, vascular invasion, lymphatic permeation, skin or nipple involvement, perineural spread, infiltration into the soft tissues and tumor necrosis. Our Cancer Registry maintained follow-up information on these patients including any additional treatment and results. The results of their follow-up were correlated with the pathologic analysis. Three patients were lost to follow-up. Poor prognosis was associated with a combination of several patho-

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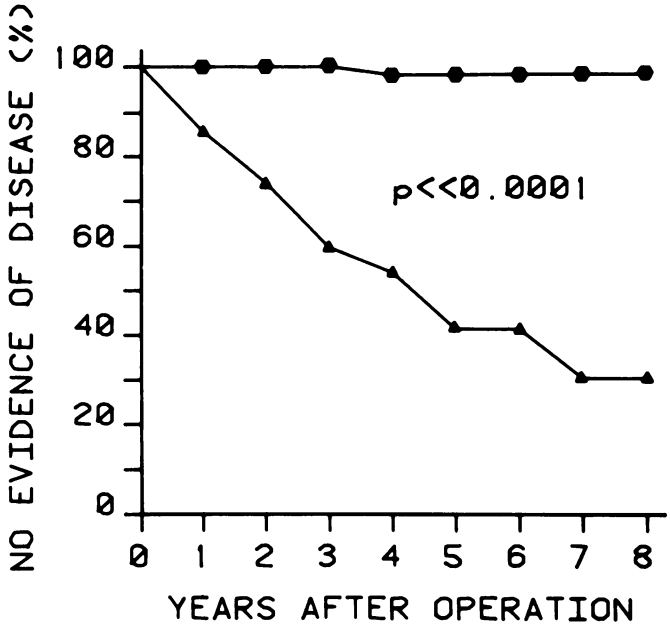

FIG. 1. Graphic presentation of the influence of histologic markers on disease free interval in 203 patients with $T_1N_0M_0$ breast cancer. Risk criteria on the presence of 1 to 4 markers. There is a high statistical significance. ●—● 109 patients not meeting risk criteria. ▲—▲ 94 patients meeting risk criteria.

logic characteristics—poor cytologic differentiation, lymphatic permeation, blood vessel invasion and invasion of the tumor into the surrounding tissues.

Tumors were designated high grade (poor cytologic differentiation) when they possessed certain characteristics: 1) variation in nuclear size and chromatin clumping, 2) high rate of mitotic activity, 3) irregular nuclear membranes and 4) a single cell pattern of invasion (except in cases of lobular carcinoma).

The presence of nests of tumor cells within lymphatic spaces was required for our diagnosis of lymphatic permeation.

Tumor thrombi within the lumen or invasion of the walls of blood vessels by malignant cells were categorized as vascular invasion.

Although most carcinomas of the breast invade the surrounding tissue to some extent, some types are more apt to be circumscribed than others. We categorized the tumors as poorly circumscribed when there was an irregular pattern of invasion of the carcinoma into adjacent tissues. The evaluation was based on the gross and microscopic appearances of the tumor.

Results

The 203 ($T_1N_0M_0$) tumors were comprised of 35 high grade adenocarcinomas, 153 moderately differentiated adenocarcinomas, six medullary, four mucinous and five lobular carcinomas. Two sarcomas were excluded from the study.

Ninety-four of the 203 tumors had one to four of the above histologic characteristics; 109 had none. Among the 109 patients who were categorized as good risks, there were two treatment failures (2%). In the group of 94 patients with any high risk histologic characteristics there were 47 treatment failures (50%) (Fig. 1).

The most common histologic characteristic was lymphatic permeation which was present in 73 tumors (36%). Blood vessel invasion found in 40 tumors (20%), was never found as an isolated characteristic and occurred only in combination with one or more of the other characteristics in the more malignant tumors. Poor circumscription occurred in 39 tumors (19%). Thirty-five tumors (17%) were of the high grade varieties (poor cytologic differentiation). These were evenly divided through all groups with nine occurring in both the highly malignant four characteristic group and in the less aggressive one characteristic group.

Curves of "no evidence of disease" status were calculated using actuarial methods designed for the analysis of occurrence of nonfatal events.[2] The possibility that the difference between any two curves was due to chance (null-hypothesis) was tested by the chi-square method.

We have a sample of 203 patients treated for Stage I carcinoma of the breast. They are divided into two groups according to their meeting or not meeting a set of criteria of risk established by the investigators and analyzed according to their suffering or not suffering failure (Table 1): Group I consists of 109 patients who did not meet the criteria of risk and Group II consists of 94 patients who met the criteria of risk. Two of the 109 patients in Group I (did not meet criteria of risk) suffered treatment failure whereas 47 of the 94 patients in Group II (met criteria of risk) suffered treatment failure.

Treatment failure occurred in all patients when all four histologic changes were present. The tumors in the nine patients in this group recurred an average of 12 months after operation and most died shortly thereafter (Fig. 2). Many of these patients had micro-

TABLE 1. *Contingency Table*

Groups	Variable 1 (Treatment Failure)	Variable 2
Group I (did not meet criteria) 109 patients	2	107
Group II (met criteria) 94 patients	47	47

X^2 (one degree of freedom) = 63.9. $p \ll 0.0001$. There is a very highly significant statistical difference between Groups I and II.

scopic involvement of the skin which was not evident grossly.

When three histologic changes were present, the results were only slightly better (Fig. 2). Treatment failure occurred in 15 of the 20 patients (75%) in this group an average of 26 months after operation with substantially longer survival rates. There was a significant difference in treatment failure when compared to the group with four histologic changes (Fig. 2).

The results were similar when only two histologic changes were present (Fig. 2). Sixteen failures occurred in the 26 patients (60%) an average of 28 months after operation. There was no significant difference in treatment failure when compared to the group with three histologic changes.

The tumors with only one change present were less aggressive (Fig. 2). Eight treatment failures occurred among the 39 patients (20%). They appeared an average of 41 months after operation. It is quite possible more will occur with a longer follow-up. No single marker predominated among the recurrences in this group which were divided between poor cytologic differentiation, lymphatic permeation and soft tissue invasion. There was a significant difference between the treatment failures in this group and the group with two histologic changes (Fig. 2).

It appeared that treatment failure was influenced by adjuvant therapy. To better measure the effect of surgical treatment on those tumors with histologic changes, the patients who also received some form of adjuvant treatment were eliminated from the group and restudied.

Among those patients treated surgically 32 of the 34 (94%) patients with four, three or two markers had treatment failure an average of seven, 18 and 25 months after operation.

In this study, pathologic changes were an effective means of earmarking those tumors which were likely to recur. Studies are in progress which will better delineate the effect of treatment on both treatment failure and survival.

We reviewed the histologic picture and the clinical course of larger lesions which had not metastasized ($T_2N_0M_0$) and ($T_3N_0M_0$). While histologic changes were present in most cases, they did not correlate with the clinical course of the ($T_2N_0M_0$) and ($T_3N_0M_0$) lesions as well as they did with the course of the ($T_1N_0M_0$) tumors. Treatment failure occurred more commonly in larger lesions even when they showed none of the histologic changes. The changes were best able to separate the bad prognosis lesions at the $T_1N_0M_0$ level.

The average age of the 109 patients without pathologic changes was 68 years. Twenty-four of the 109 patients were under 50 years old. The average age of

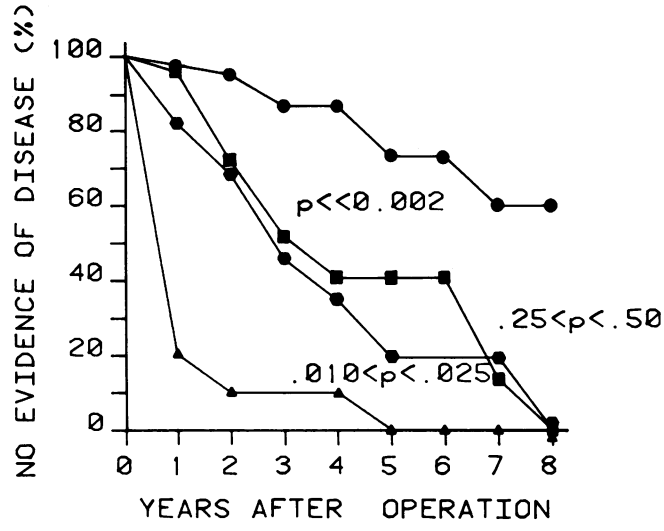

FIG. 2. Carcinoma of the breast ($T_1N_0M_0$) in 94 patients meeting risk criteria to various extents. Graphic presentation of the cumulative influence of the histologic markers on disease free interval. + denotes a single histologic marker. The p probability is statistically significant between the curve of + and those of ++ and +++. It is not significant between the curves of ++ and +++ and again is significant between the curves of ++ and +++ and the curve of ++++. ●+ (39 patients) ■++ (26 patients) ● +++ (20 patients) ▲++++ (9 patients).

the 94 patients with one to four histologic changes was 61. Twenty-seven of the 94 patients were under 50 years old. Sixteen failures occurred in the 27 patients under 50 years of age with histologic changes (60%) while the other 28 failures occurred in the 67 patients over 50 whose tumors had histologic changes (42%). These figures are not statistically significant.

Discussion

Surgeons have been concerned for many years because 20–40% of what they considered good risk patients eventually become treatment failures within 10 years.[9,10] As long as there was no way to separate the potential problems, any prospective studies would have to be applied to all the cases, making an unrealistically large sample necessary.

Delineation of the high risk group will make prospective studies on this group possible, hopefully with good results. Concern with this ill-fated group in a Stage I category has interested many investigators recently. The concept that these patients have been categorized $T_1N_0M_0$ when many may have undetected micrometastases has been broached and, in at least three studies, documented.

In 1948 Saphir and Amromin[13] restudied the axillary nodes in 30 patients in whom routine processing failed to disclose metastases and found tumor in ten patients by examining alternate serial sections. Some of these were micrometastases.

Pickren, in 1961,[12] in a similar study of 51 patients found tumors in 22% of the patients previously considered negative. Fisher, et al.[6] found occult metastases in 24% of the lymph nodes which after "routine" pathological examination were regarded as negative for metastases in 78 $T_1N_0M_0$ cases.

In none of the three studies were researchers able to correlate their findings with any change in prognosis. It is of interest that 24% of the patients studied died of their disease or are living with recurrence regardless of the presence of occult metastases.

None of Fisher's patients whose occult metastases manifested as tumor emboli in capsular lymphatics died from their disease. On the other hand, five of the patients with lesions that presented as "true" metastases in the substance of the nodes died of the disease five years later. Yet four with such metastases were free of disease five years later. We have done no studies on micrometastases and are unable to contribute to this point.

All of the characteristics used in our categorization have been considered significant by various authors. Fisher[5,7] mentioned all of these characteristics in the 16 histopathologic characteristics with which they correlated the presence or absence of occult metastasis. The Memorial group[3] considered lymphatic invasion of some, but limited, significance. However, no one considered the histologic changes as having a cumulative effect. Nime, et al.[11] found the incidence of distant metastases significantly greater in patients designated as having Stage I disease after routine pathologic study who exhibited intralymphatic tumor emboli as opposed to those (matched controls) who did not. Bonadonna[4] also regarded this as an important prognostic discriminant in breast cancer since detection of such emboli would warrant the use of chemotherapy in those patients who might not otherwise receive such adjunctive therapy.

The experiences of Fisher and Bonadonna would suggest chemotherapy as the most desirable adjuvant. On the other hand, if one subscribes to the study of Huvos, et al.,[18] who demonstrated a step-like progression up the axilla, radiotherapy might be the preferable treatment. Now that we have learned to categorize the poor risk Stage I lesions, we are retrospectively reviewing our experience with the specific purpose of weighing the impact of the various types of operations and adjuvant therapy on the course of those tumors with unfavorable histologic changes.

Fisher found age to be the only good correlation with prognosis in the National Surgical Adjuvant Breast Program (NSABP) patients. Age did not correlate with prognosis as well as the histologic changes in our patients.

The current study allows a three to eight year follow-up. Since a large percentage of the treatment failures occur before 30 months, follow-up of as little as three years was included even though more failures will occur. The present method of reporting on the specimens was adopted in 1971 by our Pathology Department in conformity with the standards established by the NSABP. These reports detail all the data necessary for histologic classification. We elected to restrict this initial report to those tumors where the interpretation was made at the time of operation and no prejudice as to long-term clinical response was possible.

This type of categorization is widely available. It can be carried out by a competent Pathologist in any hospital laboratory with the equipment currently on hand.

References

1. Adair, F., Berg, J., Jonbert, L. and Robbins, G. F.: Long Term Followup of Breast Cancer Patients: One 30 Year Report. Cancer, 33:1145, 1974.
2. Anderson, R. P., Boncheck, L. I., Grunkemeier, G. L., et al.: The Analysis and Presentation of Surgical Results by Actuarial Methods. J. Surg. Res., 16:224, 1974.
3. Berg, J. and Robbins, G. F.: Factors Influencing Short and Long Term Survival of Breast Cancer Patients. Surg. Gynecol. Obstet., 122:1311, 1966.
4. Bonadonna, G.: A New Prognostic Factor in Breast Cancer. Am. J. Surg. Pathol. I:73, 1977.
5. Fisher, E. R., Gregorio, R. M. and Fisher, B.: The Pathology of Invasive Breast Cancer. A Syllabus Derived from the Findings of the National Surgical Adjuvant Breast Project (Protocol #4) Cancer, 36:1, 1975.
6. Fisher, E. R., Swanidoro, S., Lee, C. H., et al.: Detection and Significance of Occult Axillary Node Metastases in Patients with Invasive Breast Cancer. Cancer, 42:2025, 1978.
7. Fisher, E. R., Polekar, A., Rockette, H., et al.: Pathologic Findings from the National Surgical Adjuvant Breast Project (Protocol #4) Cancer, 42:2032, 1978.
8. Huvos, A. G., Hutter, R. V. P. and Berg, J. W.: Significance of Axillary Macrometastasis & Micrometastases in Mammary Cancer: Ann. Surg., 173:44, 1971.
9. Malinin, T. and Lumb, G.: Survival of Patients with Carcinoma of Breast Without Lymph Node Metastasis in Relation to the Tumor Types. J. Surg. Oncol. 9:221, 1977.
10. Moore, F. D.: The Breast p. 265 in Management of Patient with Cancer, Nealon, T. F. Jr., Second edition. Philadelphia, W. B. Saunders. 1976. (ed).
11. Nime, F. A., Rosen, P., Thaler, H., et al.: Prognostic Significance of Tumor Emboli in Intramammary Lymphatics in Patients with Mammary Carcinoma. Am. J. Surg. Pathol. I, No. 1 March 1977. p. 25.
12. Pickren, J. W.: Significance of Occult Metastases. A Study of Breast Cancer. Cancer, 14: 1266, 1961.
13. Saphir, O. and Amromin, E. D.: Obscure Axillary Lymph Node Metastases in Carcinoma of the Breast. Cancer, I: 233, 1948.