Prognostic Significance of Tumor Cell Proliferation Rate as
Determined by the MIB-1 Antibody in Breast Carcinoma:
Its Relationship with Vimentin and p53 Protein

Wenancjusz Domagala, Maciej Markiewski,
Barbara Harezga, Andrzej Dukowicz, and
Mary Osborn

Department of Pathology, Medical Academy, 1 Unii Lubelskiej St.,
7344 Szczecin [W. D., M. M.] Poland; Department of Oncology,
Medical Academy, 4 Paderewskiego St., 9359 Lodz [B. H., A. D.],
Poland; and Department of Biochemistry, Max Planck Institute for
Biophysical Chemistry, Am Fassberg 11, D-37077 Goettingen,
Germany [M. O.]

ABSTRACT

The prognostic value of tumor cell proliferative activity as
measured by the MIB-1 monoclonal antibody in invasive
ductal not otherwise specified breast carcinomas was deter-
mined for 186 patients, including 111 with no axillary node
involvement. The MIB-1 antibody detects the Ki-67 antigen
in microwave-processed paraffin sections of the formalin-
fixed tumors. The mean MIB-1 score was 16% for all tu-
mors, 16% for the node-negative group, and 15% for the
node-positive group. In univariate survival analysis, the
MIB-1 score (dichotomized, ≤10 versus ≥10%) predicted
overall 5-year survival in all of these groups. The mean
MIB-1 score was significantly higher in vimentin- and p53
protein-positive tumors (P > 0.001) than in negative ones.
The impact of vimentin expression and of p53 positivity on
the prognostic significance of the tumor cell proliferation
rate was assessed. Vimentin was associated significantly with
poor 5-year survival in the entire cohort, and a particularly
strong association was found in the node-negative group.
p53 had a weak but statistically nonsignificant influence on
survival. In a multivariate analysis using the Cox propor-
tional hazards model, vimentin (P = 0.0002) was the only
independent prognostic factor in node-negative patients.
In contrast, the MIB-1 score (P = 0.009) was the only indepen-
dent prognostic factor in the node-positive group. Therefore,
ode-negative patients with vimentin-positive tumors and
node-positive patients with tumors with high proliferation
rates might be appropriate candidates for early adjuvant
chemotherapy.

INTRODUCTION

Axillary lymph node status is regarded as the single most
important prognostic indicator in breast cancer. However, addi-
tional prognostic factors are needed, because the majority of
breast cancer patients currently diagnosed are axillary node
negative, yet 25–35% will relapse (1, 2). Tumor cell prolifera-
tion as measured by methods such as tritiated thymidine uptake
(3, 4), flow cytometry (5), mitotic counts (6), and assessment of
proliferation-associated antigens (7–12) is regarded as a strong
indicator of poor prognosis in breast cancer. However, it seems
to be interrelated with other prognostic factors. For example,
both vimentin positivity (13, 14) and p53 protein positivity (15,
16) have been associated with an increased tumor cell prolifera-
tion rate, and all three factors seem to have prognostic signif-
icance in breast cancer (4, 16–21). From a practical point of
view, it is not known which one or which combination of these
markers should be used to obtain maximum reliable prognostic
information.

Our interest in this study was 2-fold. First, we wanted to
use the MIB-1 antibody in a prognostic study in invasive ductal
NOS breast cancer, with the emphasis on node-negative pa-
tients. The MIB-1 antibody was generated against recombinant
parts of the Ki-67 antigen (22). Ki-67 is a nuclear antigen
present in G1, S, G2, and M phases of the cell cycle but not in
resting cells (23). The MIB-1 antibody is particularly useful in
the evaluation of the growth fraction of tumor cells, because it
immunostains formalin-fixed, paraffin-embedded sections, pro-
vided they have been heated in a microwave oven (22). A
significant correlation was found between the MIB-1 labeling
index and that of Ki-67 on frozen sections (24) and between the
MIB-1 and mitotic tumor indices and the Scarff-Bloom-Rich-
dardson histological grade of breast carcinomas (25). Our second
aim was to determine whether the proliferation rate, vimentin
positivity, and p53 positivity of tumor cells are dependent or
independent prognostic indicators. Although vimentin (13, 14)
and p53 protein (15, 16) are related to the cell proliferation rate,
the prognostic effect of p53 protein seems to be related mainly
to the proliferation rate of tumor cells (16), whereas vimentin
is also associated with increased invasiveness of breast cancer cell
lines (26). This is also reflected in vivo, in which, particularly in
node-negative patients, those with vimentin-positive tumors
have a significantly higher probability of visceral relapse (19).
A similar association between p53 status and visceral metastases
was not found (19). Therefore, we hypothesized that in node-
negative patients, the prognostic effect of vimentin, but not that
of p53 protein, might be much stronger than that of the cell
proliferation rate. Therefore, we assessed tumor cell prolifera-
tion by immunohistochemistry using the novel MIB-1 mono-
clonal antibody on microwave-treated paraffin sections of forma-
lin-fixed, invasive, ductal NOS breast carcinomas in which the

Received 5/30/95; revised 8/10/95; accepted 8/17/95.
1 This work was supported by European Union Grant CT93-0234.
2 To whom requests for reprints should be addressed. Phone: +49-551-
201-1486; Fax: +49-551-201-1578.

3 The abbreviations used are: NOS, not otherwise specified; ER, estro-
gen receptor.
vimentin and p53 protein statuses of the same tumors were already known. The results were compared with survival curves for a 5-year period.

MATERIALS AND METHODS

Patients. Formalin-fixed and paraffin-embedded tumor samples from 186 unselected female patients with primary invasive ductal NOS breast cancer who underwent mastectomy with lymph node dissection between 1980 and 1987 were examined. These were retrieved from the files of the Department of Oncology, Medical Academy of Lodz. Clinical follow-up was available for at least 60 months. Histological typing was performed as described by Millis and Girling (27), and histological grading was according to Bloom and Richardson (28). The computerized database contained the age of the patient, the number of positive axillary lymph nodes, the size of the tumor, histological type and grade, the stage of the disease at diagnosis, the treatment protocol, and the date of the last checkup or death. In addition, vimentin and p53 protein statuses of the tumor were also on file. Some patients analyzed in this study were included in previous studies on vimentin expression and survival (18) and on p53, vimentin, survival, and sites of metastases (19). There were 111 axillary lymph node-negative and 75 lymph node-positive patients. Lymph node-negative patients underwent either only mastectomy with removal of the axillary lymph nodes (45 patients) or mastectomy with removal of the nodes followed by radiation therapy (19 patients), chemotherapy (22 patients), hormone therapy (3 patients), radiation therapy and chemotherapy (7 patients), or combinations of radiation therapy, chemotherapy, and hormone therapy (11 patients). Four patients were treated by quadrantectomy with removal of axillary nodes followed by radiation therapy. Lymph node-positive patients underwent either only mastectomy with removal of the axillary lymph nodes (6 patients) or mastectomy with removal of the nodes followed by radiation therapy (22 patients), chemotherapy (4 patients), hormone therapy (2 patients), radiation therapy and chemotherapy (22 patients), or combinations of radiation therapy, chemotherapy, and hormone therapy (18 patients). One patient underwent quadrantectomy with removal of axillary nodes followed by radiation therapy. As in all studies of this type, the use and kind of adjuvant therapy have to be taken into account in interpreting the results.

Immunohistochemistry. Sections were deparaffinized, immersed in citrate buffer, and heated in a microwave oven according to Cattoretti et al. (22). The sections were incubated with MIB-1 monoclonal antibody (Dianova, Hamburg, Germany) diluted 1:30 for 45 min at room temperature. Sections were washed and reacted with biotinylated rabbit antihouse antibody and streptavidin peroxidase (Histostain-SP kit; Zymed Laboratories, Inc., San Francisco, CA). The sections were washed and then lightly counterstained with hematoxylin. Areas with the highest numbers of MIB-1-positive cells were identified by scanning sections at low magnification. These areas occurred mostly at the periphery of tumors. Counts were started in these areas, and then additional contiguous fields were selected randomly until at least 500 tumor cells were counted using a 10 x 10 square ocular grid and x400 magnification. The results were scored as the percentage of tumor cell nuclei reactions with the MIB-1 antibody. The MIB-1 score was assessed independently by two pathologists (W. D. and M. M.) without knowledge of other data of the patient. The results were combined, and the mean was used. The MIB-1 scores determined by W. D. correlated highly with those determined by M. M. (linear regression analysis, r = 0.85; P > 0.0001; 95% confidence interval).

Statistical Analysis. The association between MIB-1 score and vimentin and p53 statuses was assessed by the Student t test. Univariate survival analysis was based on the Kaplan-Meier product limit estimates of survival distribution. Differences between survival curves were tested using the $\chi^2$ statistic. The Cox proportional hazards model was used in multivariate analysis of the survival data and for assessment of relative risk ratios. All data were analyzed with the SAS computer program PHREG (version 6.08; SAS Institute, Inc., Cary, NC). The multivariate analysis included only those cases in which complete sets of data were available, i.e., 177 for all, 106 for node-negative, and 71 for node-positive patients.

RESULTS

MIB-1 Staining in Breast Carcinomas

All tumor cells in which red color was found in the nuclei or nucleoli were scored as positive regardless of staining intensity (which in general was strong). MIB-1 positivity was found exclusively in the nuclei or nucleoli, with some variation in intensity in different cells within the same section. Mitotic figures were stained strongly in all cases. Although the distribution of positive nuclei was heterogeneous, immunoreactive tumor cells could be distinguished easily from nonreactive tumor cells and benign cells. All 186 tumors were positive for MIB-1, but considerable intertumoral and intratumoral variations of MIB-1 scores were found. The mean MIB-1 score for the whole series of tumors was 16% (SD, 14%; range, 0.1–60.4%; median, 12%); for tumors from axillary lymph node-negative patients, the mean score was 17% (SD, 14%; range, 0.1–52.7%; median, 14%); and for tumors from node-positive patients, the mean score was 15% (SD, 15%; range, 0.4–60.5%; median, 10%). The mean MIB-1 score in our study, i.e., 16.2%, falls within the range of values reported with the use of the MIB-1 antibody (12, 20–24%; Refs. 24, 25, and 29) as well as the Ki-67 antibody on frozen sections of breast carcinomas, i.e., between 7.2 and 22% (12, 30–32). The considerable variability in MIB-1 and Ki-67 scores in the different studies has been attributed to the use of different evaluation methods and to the inherent variability between individual patients and also between distinct high-power fields from the same tissue section (12). Nevertheless, Wintzer et al. (12) found a high degree of correlation between results obtained by two different counting methods, i.e., 10 random high-power counts versus the area with the highest labeling density count.

To correlate the MIB-1 score with vimentin and p53 statuses and to analyze the relationship to survival, a 10% cutoff level for the MIB-1 score was chosen to separate the high-risk group from the low-risk breast cancer. In previous survival studies using the Ki-67 antibody, various cutoff levels were used, e.g., 7.5% (9), 9% (8), 10% (10), 13% (11),
Correlation of MIB-1 Scores with Vimentin and p53 Protein

The mean MIB-1 score was significantly higher in vimentin-positive than in vimentin-negative tumors \( (P < 0.001 \text{ for all and for axillary node negative-patients}; P < 0.01 \text{ for node-positive patients}) \). p53-positive tumors also had a significantly higher mean MIB-1 score than those cancers that did not express this protein \( (P < 0.001 \text{ for all and for node-negative and node-positive patients}; \text{Table 1}) \).

Prognostic Significance of MIB-1 Score with Respect to Vimentin and p53 Protein Status

All Patients. One hundred sixteen (61%) patients survived 5 years. The mean follow-up time for these patients was 88 months. In the univariate survival analysis, the MIB-1 score \( (\text{dichotomized, } \leq 10 \text{ versus }>10\%) \) and vimentin predicted 5-year survival \( (\text{Table 2}) \). Classical prognostic factors such as lymph node status, tumor size, and histological grade were also strong indicators of prognosis \( (\text{Table 2}) \). Survival curves also show that a high MIB-1 score is associated with poor survival of patients at 5 years in the entire cohort \( (P < 0.01) \), in node-negative patients \( (P < 0.05) \), and in node-positive patients \( (P < 0.01; \text{Fig. 1, A-C}) \).

When all the factors listed in Table 2 were tested in the Cox proportional hazards model for their relationship with overall survival, the four factors selected by the model as independent predictors of survival at 5 years were node status, tumor size, MIB-1 score \( (\text{dichotomized, } \leq 10 \text{ versus }>10\%) \) and vimentin status \( (\text{Table 3}) \).

Axillary Node-negative Patients. The results of univariate survival analysis indicate that vimentin status, tumor size, and MIB-1 score \( (\text{dichotomized}) \) predict 5-year survival \( (\text{Table 2}) \). Survival curves for node-negative patients also show that a high MIB-1 score was associated significantly with poor sur-
Table 2 Prognostic factors predicting 5-year survival of patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>All patients</th>
<th>Node-negative</th>
<th>Node-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIB-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10%</td>
<td>80</td>
<td>59</td>
<td>74</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>106</td>
<td>57</td>
<td>54</td>
</tr>
<tr>
<td>Vimentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>145</td>
<td>96</td>
<td>66</td>
</tr>
<tr>
<td>Positive</td>
<td>41</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>p53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>129</td>
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</tr>
<tr>
<td>I + II</td>
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<td>66</td>
<td>72</td>
</tr>
<tr>
<td>III</td>
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<td>50</td>
<td>64</td>
</tr>
<tr>
<td>Size (mm)</td>
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<td></td>
</tr>
<tr>
<td>≤30</td>
<td>57</td>
<td>48</td>
<td>84</td>
</tr>
<tr>
<td>&gt;30</td>
<td>127</td>
<td>68</td>
<td>54</td>
</tr>
<tr>
<td>Age (yr)</td>
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<td></td>
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</tr>
<tr>
<td>&lt;50</td>
<td>60</td>
<td>41</td>
<td>68</td>
</tr>
<tr>
<td>≥50</td>
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<tr>
<td>Negative</td>
<td>111</td>
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<td>72</td>
</tr>
<tr>
<td>Positive</td>
<td>75</td>
<td>36</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 3 Relationship of prognostic factors to reduced 5-year overall survival

Results of the Cox proportional hazards model analysis for all (n = 177) and for node-negative (n = 106) and node-positive (n = 71) patients. Other factors tested in the Cox model were histologic grade, p53 status, and age of the patient.

<table>
<thead>
<tr>
<th>Factor</th>
<th>All patients</th>
<th>Node-negative</th>
<th>Node-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIB-1</td>
<td>2.06</td>
<td>0.005</td>
<td>2.43</td>
</tr>
<tr>
<td>Vimentin</td>
<td>1.88</td>
<td>0.016</td>
<td>3.55</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>2.40</td>
<td>0.0003</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor size</td>
<td>2.28</td>
<td>0.007</td>
<td>NA</td>
</tr>
</tbody>
</table>

a RR, relative risk of death; NS, not significant; NA, not applicable.

When lymph node-negative patients were first divided by vimentin status, and then survival curves were plotted by MIB-1 score, there was no significant difference in survival for patients with tumors with high versus low proliferative activity either in the vimentin-positive (Fig. 2a, curve B versus C) or vimentin-negative subgroup, although there was a trend in the latter for highly proliferating tumors to indicate worse prognoses (curve D versus A). However, if node-negative patients were first divided according to the MIB-1 scores (high versus low) of their tumors, and then survival curves were plotted by vimentin status, vimentin expression stratified the patients significantly (curves C versus D and A versus B). Patients with vimentin-positive tumors had worse survival irrespective of low (curve B, P < 0.01) or high (curve C, P < 0.05) proliferation rate. Thus, analysis of survival curves indicates that in node-negative patients, vimentin is a stronger indicator of poor prognosis than proliferative activity of tumor cells. At 5 years, only about 50% of patients with vimentin-positive tumors survive, irrespective of whether the patients had tumors with high or low MIB-1 scores (curves C and B). In contrast, the proliferation rate only seems to play a role in the survival of node-negative patients with vimentin-negative tumors. Here, about 75% of patients with fast-proliferating tumors, i.e., MIB-1 scores >10%, survive 5 years, compared with 90% of those with MIB-1 scores ≤10%, although the difference does not reach statistical significance (χ² = 2.157).

Node-negative patients with p53-negative and slowly proliferating (MIB-1 score, ≤10%) tumors had better prognoses than those with high MIB-1 scores (Fig. 2b, curve A versus D) but the trend was not significant (χ² = 3.146). If node-negative patients with p53-positive tumors were divided by MIB-1 score (curve B versus C), survival curves differed slightly, in that patients with highly proliferating tumors had worse 5-year survival, but the difference did not reach statistical significance. When the node-negative patients were divided by MIB-1 score and p53 status (curves C versus D and A versus B), patients with p53-positive tumors had worse survival in both subgroups, but, again, the trends did not reach statistical significance.

In the Cox proportional hazards model, of all the factors listed in Table 2, only vimentin status was selected as an independent predictor of survival in node-negative patients (Table 3).
Axillary Node-positive Patients. The univariate survival analysis shows that a high MIB-1 score and high histological grade are associated significantly with 5-year survival of patients (Table 2). Survival curves also show a significant prognostic difference when node-positive patients were divided according to proliferation rate ($P < 0.01$; Fig. 1C).

When this group of patients was divided by MIB-1 score and survival curves plotted by vimentin status, a significant negative correlation of vimentin expression and survival was seen only in patients with slowly proliferating tumors ($P < 0.05$, Fig. 3a, curve $A$ versus $B$; compare with curve $C$ versus $D$). When the node-positive patients were divided by vimentin status and survival curves were plotted by proliferation rate, there was a negative prognostic significance of high MIB-1 score for patients with vimentin-negative tumors ($P < 0.01$, curve $A$ versus $D$). An even stronger poor prognostic effect of high MIB-1 score was seen in node-positive patients with p53-negative tumors (Fig. 3b, curve $A$ versus $D$; $P < 0.001$). When node-positive patients were divided by MIB-1 score and survival curves were plotted by p53 status, the trend emerged for worse survival of patients with p53 positive, slowly proliferating tumors and better survival of patients with p53-positive, rapidly proliferating tumors; however, both trends did not reach statistical significance (curves $A$ versus $B$ and $C$ versus $D$, not significant).

DISCUSSION

Our data show that the tumor cell proliferation rate as determined by MIB-1 activity on paraffin sections is associated significantly with 5-year overall survival in the entire cohort and in the node-negative and node-positive subsets of patients. Our results confirm reports that demonstrated a significant correlation between the proliferation rate of cancer cells as determined by Ki-67 immunostaining in frozen sections (7, 9–12, 33–35) or by the Ki-S1 antibody in paraffin-embedded tissue (36) and survival of breast cancer patients. Most of these studies report on short-term, disease-free survival. Of 12 studies published to date on Ki-67 and prognosis, only two examined more than 100 node-negative patients. Although Railo et al. (10) and Gasparini et al. (9) examined 196 and 164 such patients, respectively, they reported on shorter survival (4 and 3 years, respectively). There-
fore, our group of 111 node-negative patients with 5-year survival, although relatively small, is comparable in size to that used in previous studies with Ki-67 antibodies. The only report on Ki-67 and 5-year survival (11) is based on 42 node-negative patients, whereas a very recent article also examines MIB-1 staining and long-term survival (37). Our data are also in agreement with studies documenting the significant prognostic value of the proliferation rate measured by thymidine labeling (3, 4) or flow cytometry (5). However, because of the relatively small size of the study population, and because the results were not validated in an independent set of patients, our results should be viewed as a pilot study.

Using a multivariate Cox analysis of survival we found that the tumor cell proliferation rate, i.e., MIB-1 score, provided independent significant prognostic information in the entire cohort of patients as well as in the node-negative subset. In the latter group, it was the only independent predictor of overall survival at 5 years.

In contrast, for node-negative patients, the MIB-1 score was not an independent predictor of overall survival. The proliferation rate of tumor cells ceased to be a significant factor after vimentin was taken into account in the Kaplan-Meier survival curves (Fig. 2a, curves B versus C and A versus D) and did not enter the Cox model. Vimentin status was the only independent predictor of overall survival at 5 years in this group.

Attempts to use other proliferation-associated factors, such as the ER or epidermal growth factor receptor, to stratify node-negative patients have been relatively unsuccessful. For instance, Railo et al. (10) saw no difference in disease-free survival between node-negative patients in the categories ER negative and Ki-67 >10% and ER positive and Ki-67 ≤10%, although they were able to demonstrate a 35% difference in 4-year survival (P < 0.005) between stage II patients in these two groups. Toi et al. (38) also were unable to stratify node-negative patients into high- and low-risk groups using the epidermal growth factor receptor, another marker linked closely to cell proliferation.

Attempts to stratify node-negative patients using p53 have yielded conflicting results. Using immunohistochemistry, a significant association with shortened survival (16, 17, 21), a small but statistically nonsignificant negative effect (19, 39), and a positive effect (40) of p53 positivity on survival of node-negative patients have been reported. No significant difference in survival between patients with mutant and wild-type p53 tumors has been found (41). In this report, we show that for our series of breast carcinomas, p53 positivity is not an independent predictor of 5-year survival when tested against the proliferation rate of tumor cells and vimentin expression. This is in agreement with the results of Isola et al. (16), who showed that p53 had independent prognostic value in a multivariate analysis only in the absence of the S-phase fraction. If the S-phase fraction was included in the analysis, only S-phase and tumor size emerged as independent predictors of overall survival. However, Alfred et al. (17) reported that positive p53 and S-phase were independent predictors of reduced disease-free survival despite the strong direct correlation between p53 positivity and tumor proliferation rate. p53 protein is associated strongly with proliferation but not necessarily with invasion. Recently, Hsiao et al. (42) have shown that in acute lymphocytic leukemias, some specific p53 mutations were associated with increased invasiveness, and others were not. Thus, tumors determined by immunohistochemistry to be p53 positive are most likely a heterogenous mixture of growth-promoting and ineffective mutations, and, thus, it may be important to determine the precise p53 mutations present in each tumor rather than only p53 positivity or negativity.

We have shown that vimentin expression is a strong indicator of poor prognosis in node-negative patients as well as in the whole cohort of patients with invasive ductal NOS breast carcinoma (18). The prognostic value of vimentin in the whole cohort of patients has been confirmed in two reports (20, 43).

Why is the proliferation rate of tumor cells a less useful prognostic indicator than vimentin positivity in node-negative patients? This may be due to the association of vimentin expression not only with proliferation but also with the invasiveness of tumor cells both in vitro (26, 44–47) and in vivo (19). Poor prognoses in a subset of node-negative patients depends on hematogenous micrometastases, particularly on visceral ones i.e., to the brain, lungs, and liver, that were not detected at the time of the first operations. During tumor progression, breast carcinoma cells probably go through several stages in a complex sequence of events that lead ultimately to metastasis. One event leading to metastasis also may induce vimentin expression (48), although vimentin is probably associated with only one of several different pathways leading to the metastatic phenotype, because vimentin-negative tumors also metastasize. Direct support for the idea that vimentin-positive tumors may be more invasive is given by data showing that in node-negative patients, vimentin-positive primary invasive ductal NOS breast carcinomas metastasized 3.5 times as often as to the lung, liver, and brain as did vimentin-negative primary carcinomas (19). Thus, vimentin expression in breast cancer might be associated with the expression of genes involved in the metastatic process. However, the molecular basis of the selective advantage offered to tumor cells by events that are associated with vimentin expression is not known. Although an increased proliferation rate of tumor cells also might contribute indirectly to metastasis, e.g., because of evolving clones that have a higher probability of acquiring a metastatic phenotype, our data suggest that this is not sufficient for proliferation to become a prognostic factor independent of vimentin expression in node-negative patients.

The node-positive patients are a mixed group of those who have only regional and those who may have widespread although undetected dissemination of tumor cells at the time of surgery. One may expect that in this group, the higher the proliferation rate of tumor cells, the worse the prognosis. Our results show that, indeed, it is the node-positive group in which the determination of tumor cell proliferation rate is important, because tumors with high proliferation rates signify poor prognoses irrespective of vimentin or p53 status. The proliferation rate, vimentin status, p53 status, histological grade, and size of tumors were tested in a multivariate Cox analysis for their relationship with 5-year overall survival of patients with invasive ductal NOS breast carcinoma. Although the study population is relatively small (186 patients), the results identify the vimentin status in node-negative patients and the proliferation rate of tumor cells in node-positive patients as important prognostic factors.
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